(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 612 743 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **94301341.7**

(22) Date of filing : **25.02.94**

(51) Int. Cl.[5] : **C07D 413/12**, A61K 31/42, C07D 417/12, A61K 31/425, A61K 31/44, C07D 413/14, // (C07D413/12, 263:00, 263:00)

(30) Priority : **26.02.93 JP 38236/93**
09.08.93 JP 197304/93

(43) Date of publication of application :
31.08.94 Bulletin 94/35

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

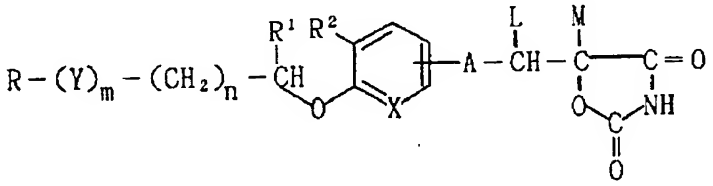
(71) Applicant : **TAKEDA CHEMICAL INDUSTRIES, LTD.**
1-1, Doshomachi 4-chome
Chuo-ku, Osaka 541 (JP)

(72) Inventor : **Sohda, Takashi**
27-20, Higashikanmaki 2-chome
Takatsuki, Oksa 569 (JP)
Inventor : **Ikeda, Hitoshi**
3-13-712, Nishi-iwata 3-chome
Higashiosaka, Osaka 578 (JP)
Inventor : **Momose, Yu**
2-1-213, Sumiregaoka 3-chome
Takarazuka, Hyogo 665 (JP)
Inventor : **Imai, Sachiko**
51-113, Kawashimahigashidai-cho
Nishikyo-ku, Kyoto 615 (JP)

(74) Representative : **Laredo, Jack Joseph**
Elkington and Fife
Prospect House
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

(54) Oxazolidinedione derivatives, their production and use in lowering blood sugar and lipid levels.

(57) Novel 2,4-Oxazolidinedione compounds of the formula (I) :



(I),

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted ; Y is -CO-, -CH(OH) or -NR^3- (wherein R^3 is an alkyl group, which may itself be substituted) ; m is O or 1 ; n is 0, 1 or 2 ; X is CH or N ; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms ; R^1 and R^2 are each independently hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen ; L and M are each hydrogen, or L and M combine with each other to form a bond ; and
pharmaceutically acceptable salts thereof,
have excellent hypoglycemic and hypolipidemic activities, and are useful as antidiabetics or as hypolipidemic agents.

EP 0 612 743 A1

This invention relates to a novel oxazolidinedione derivative which has the effect of lowering blood sugar and lipids in blood, to a method of producing the said derivatives, and to an agent for the therapy of diabetes, which is useful in the field of pharmaceuticals.

As remedies for diabetes, various biguanide compounds and sulfonylurea compounds have so far been proposed and used. However, biguanide compounds are hardly used at present, since they cause lactic acidosis, while sulfonylurea compounds, which have a strong action of lowering blood sugar, often cause severe hypoglycemia, requiring special precautions in use.

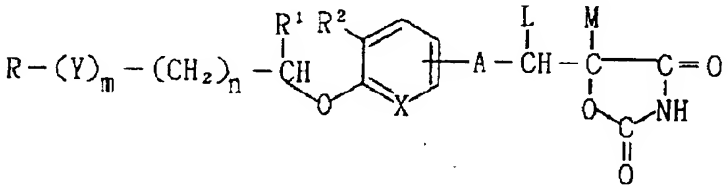
On the other hand, various thiazolidinedione derivatives and oxazolidinedione derivatives are known to lower blood sugar and blood lipids, and to be substantially free of such drawbacks.

Thus, for example, JPA H3(1991)-170478 and WO9202520-A1 describe, as 2,4-oxazolidinedione derivatives having substituents at the 5-position, a series of 5-(substituted benzyl)-2,4-oxazolidinedione derivatives; JPB S62(1987)-30993 describes 2,4-oxazolidinedione derivatives substituted with alicyclic groups at the 5-position; and JPB S63(1988)-35632 describes 2,4-oxazolidinedione derivatives substituted with, among others, a substituted aromatic ring at the 5-position.

In our study of 2,4-oxazolidinedione derivatives, we have found that certain novel 2,4-oxazolidinedione derivatives having, as substitutents at the 5-position of the 2,4-oxazolidinedione ring, a bivalent straight or branched chain hydrocarbon residue, substituted with phenyl or pyridyl, e.g., a 2-(substituted phenyl or substituted pyridyl)ethyl group, a 3-(substituted phenyl or substituted pyridyl)propyl group, a 4-(substituted phenyl or substituted pyridyl)butyl group, or a 5-(substituted phenyl or substituted pyridyl)pentyl group, are effective in lowering blood sugar and lipids in blood.

More specifically, the present invention relates to:

(1) 2,4-Oxazolidinedione derivatives represented by the general formula (I):



(I)

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH) or NR^3- (wherein R^3 is an alkyl group, which may be substituted); m is O or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each independently hydrogen or an alkyl group, or R^1 and R^2 are combined with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M are each independently hydrogen, or L and M are combined with each other to form a bond,

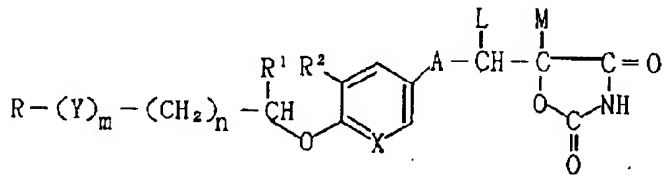
and pharmaceutically acceptable salts thereof;

(2) a medicinal composition comprising, as an effective component, a 2,4-oxazolidinedione derivative represented by the general formula (I), as defined above, or a pharmaceutically acceptable salt thereof;

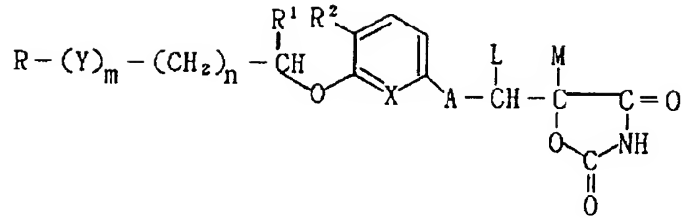
(3) the use of a compound of the formula (I), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a mammal suffering from diabetes or hyperlipidemia; and

(4) methods of producing 2,4-oxazolidinedione derivatives represented by the general formula (I) and pharmaceutically acceptable salts thereof.

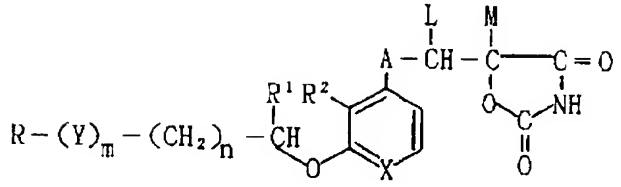
The compounds represented by the general formula (I) and their pharmaceutically acceptable salts include compounds shown by the following formulae (I-A1), (I-A2) and (I-A3):



(I-A1);



(I-A2);

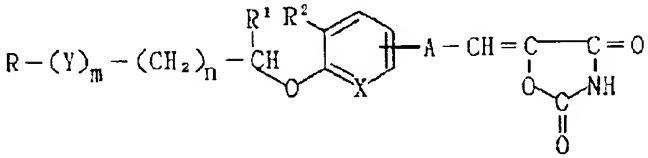


(I-A3);

wherein each symbol has the meaning given above, and their pharmaceutically acceptable salts.

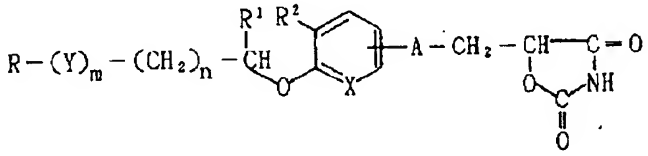
Among the compounds (I-A1), (I-A2) and (I-A3), compounds (I-A1) and (I-A2) are preferred, and compounds (I-A1) are most preferred from the viewpoints of pharmacological activity, toxicity and side-effects.

Compounds shown by the formula (I) wherein L and M are combined with each other to form a bond can be represented by the following formula (I-B1):



(I-B1)

wherein each symbol has the meaning given above. Compounds shown by the formula (I) wherein L and M are each hydrogen can be represented by the following formula (I-B_2):



(I-B2)

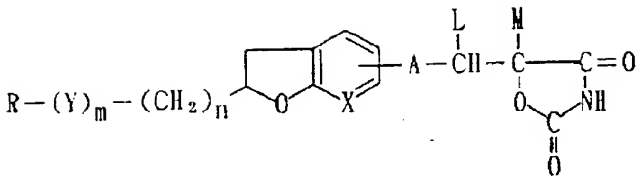
wherein each symbol has the meaning given above.

In the formula (I), alkyl groups represented by the symbols R^1 and R^2, respectively, are those having 1 to 4 carbon atoms, e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl.

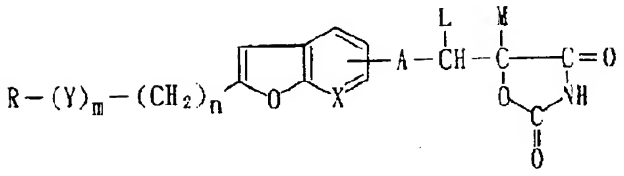
The above-mentioned general formula (I-B1) represents both (E) - and (Z) - isomers relative to the double bond at the 5-position of the 2,4-oxazolidinedione ring.

With respect to the above general formula (I), in the case where R^1 and R^2 combine with each other to form a 5- or 6-membered heterocyclic ring, optionally containing N, examples of such compounds include those represented by the following general formulae:

(1) R^1 and R^2 combine with each other to form a 5-membered heterocyclic ring [(I-C1) and (I-C2)]:



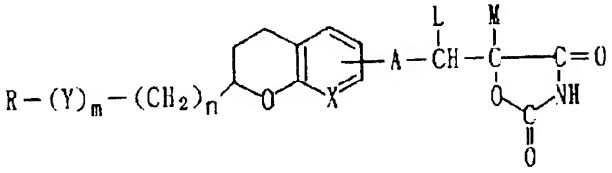
(I-C1)



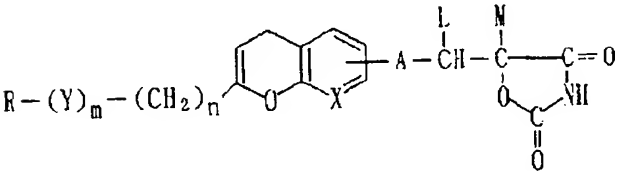
(I-C2)

[wherein each symbol has the meaning given above]

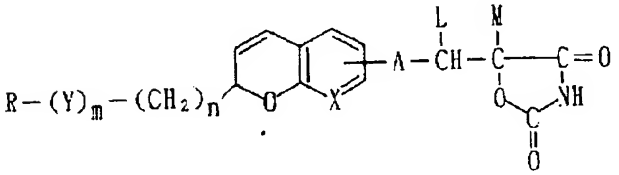
(2) R^1 and R^2 combine with each other to form a 6-membered heterocyclic ring [I-C3)-(I-C5)]



(I-C3)



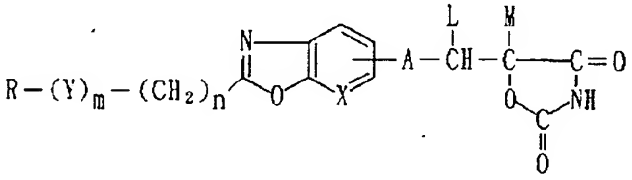
(I-C4)



(I-C5)

[wherein each symbol has the meaning given above]

(3) R^1 and R^2 combine with each other to form a 5-membered heterocyclic ring containing N [(I-C6)]:

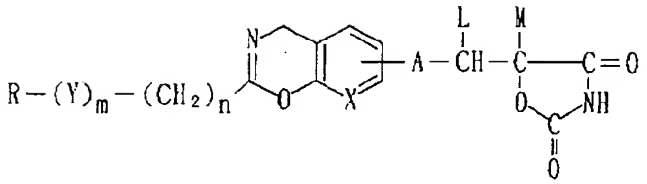


(I-C6)

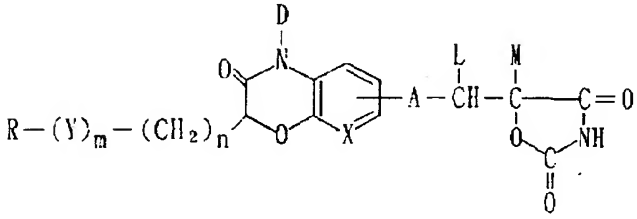
[wherein each symbol has the meaning given above]

(4) R^1 and R^2 combine with each other to form a 6-membered heterocyclic ring containing N [(I-C7) - (I-

C8)]:



(I-C7)



(I-C8)

[wherein D represents hydrogen or a lower alkyl group, and the other symbols have the meanings given above].

Among the above-mentioned compounds (I-C1) to (I-C8), those represented by (I-C1), (I-C2), (I-C3) and (I-C6) are preferred.

In the above-mentioned general formula (I), as hydrocarbon residues in the hydrocarbon residues which may be substituted shown by R, mention is made of aliphatic hydrocarbon residues, alicyclic hydrocarbon residues, alicyclic-aliphatic hydrocarbon residues, aromatic aliphatic hydrocarbon residues, aromatic hydrocarbon residues and aromatic heterocyclic-aliphatic hydrocarbons residues. As the aliphatic hydrocarbon residues, mention is made of those having 1 to 8 carbon atoms including saturated aliphatic hydrocarbon residues having 1 to 8 carbon atoms, as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and unsaturated aliphatic hydrocarbon residues having 2 to 8 carbon atoms, as exemplified by ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl; 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl. As the alicyclic hydrocarbon residues, mention is made of those having 3 to 7 carbon atoms, including saturated alicyclic hydrocarbon residues having 3 to 7 carbon atoms, as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and unsaturated alicyclic hydrocarbon residues having 5 to 7 carbon atoms, as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl. As the alicyclic-aliphatic hydrocarbon residues, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon residues, those having 4 to 9 carbon atoms, as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexenylethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl. As the aromatic aliphatic hydrocarbon residues, mention is made of phenylalkyl having 7 to 9 carbon atoms, as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and naphthylalkyl having 7 to 9 carbon atoms, as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl. As the aromatic hydrocarbon residues, mention is made of, for example, phenyl and naphthyl (α-naphthyl, β-naphthyl). As the aromatic heterocyclic-aliphatic hydrocarbon residues, mention is made of those formed by combination of the heterocyclic groups mentioned below with the above-mentioned aliphatic hydrocarbon residues, which are exemplified as follows.

In the above-mentioned general formula (I), as the heterocyclic groups in the substituted heterocyclic groups which may be substituted shown by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing one sulfur atom, nitrogen atom or oxygen atom, 5- to 6-membered heterocyclic groups containing 2 to 4 nitrogen atoms, and 5- to 6-membered heterocyclic groups containing 1 to 2 nitrogen atoms and one sulfur atom or oxygen atom. These heterocyclic groups are optionally condensed with a 6-membered ring containing one or two nitrogen atoms, a benzene ring or a 5-membered ring containing one sulfur atom. Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyr-

imidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazol-3-yl, 1,3,4-triazol-2-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, benzpyrazol-3-yl, 1H-pyrrolo[2, 3-b]pyrazin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyrazin-2-yl.

In the above-mentioned general formula (I), the hydrocarbon residue and heterocyclic residue shown by R optionally have 1 to 3 substituents at substitutable positions, respectively. As such substituents, mention is made of an aliphatic chain hydrocarbon group, an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group, a non-aromatic heterocyclic group, an halogen atom, a nitro group, an optionally substituted amino group, an optionally substituted acyl group, an optionally substituted hydroxyl group, an optionally substituted thiol group and an optionally esterified carboxyl group. As the aliphatic chain hydrocarbon group, mention is made of straight-chain or branched aliphatic hydrocarbon groups having 1 to 15 carbon atoms, for example, an alkyl group, preferably, an alkyl group having 1 to 10 carbon atoms, an alkenyl group, preferably, an alkenyl group having 2 to 10 carbon atoms, and an alkynyl group, preferably, an alkynyl group having 2 to 10 carbon atoms. Preferred examples of the alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethyl propyl, hexyl, isohexyl, 1,1-dimethyl-butyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl. Preferred examples of the alkenyl group include vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl and 5-hexenyl. Preferred examples of the alkynyl group include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. As the alicyclic hydrocarbon group, mention is made of saturated or unsaturated alicyclic hydrocarbon groups having 3 to 12 carbon atoms, for example, a cycloalkyl group, a cycloalkenyl group and a cycloalkadienyl group. Preferred examples of the cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2.]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.1]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl. Preferred examples of the cycloalkenyl group include 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-l-yl. Preferred examples of the cycloalkadienyl group include 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-l-yl and 2,5-cyclohexadien-1-yl. By the said aryl group is meant a monocyclic or condensed polycyclic aromatic hydrocarbon group. Preferred examples of the aryl group include those having 6 to 14 carbon atoms such as phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. Among them, phenyl 1-naphthyl and 2-naphthyl are preferred.

Preferred examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups, e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups, e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzoimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferred examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, pyrrolidino, piperidino, morpholino and piperazinyl. Examples of the halogen include fluorine, chlorine, bromine and iodine. Among them, fluorine and chlorine are especially preferred. The optionally substituted amino group includes both an unsubstituted amino group and substituted amino groups. As the substituted amino group, mention is made of an amino group ($-NH_2$) on which one or two alkyls having 1 to 10 carbon atoms, alkenyls having 1 to 10 carbon atoms, aromatic groups or acyl groups having 2 to 10 carbon atoms (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino and benzoylamino) is, or are, substituted. The optionally substituted acyl group includes an unsubstituted acyl group and substituted acyl groups. As the unsubstituted acyl group, mention is made of formyl and those formed by condensation of a (C_1-C_{10})alkyl, (C_1-C_{10})alkenyl or (C_6-C_12) aromatic group with a carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanoyl, cyclopentanoyl, cyclohexanoyl, cycloheptanoyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl and nicotinoyl). The substituted acyl group includes acyl groups mentioned above in connection with an unsubstituted acyl group but which have substituents(s) such as an alkyl having

1 to 3 carbon atoms, an alkoxy having 1 to 3 carbon atoms, halogen (e.g. chlorine or bromine), nitro, hydroxy, or amino. The optionally substituted hydroxyl group includes an unsubstituted hydroxyl group and substituted hydroxyl groups. As the substituted hydroxyl group, mention is made of these having, on this hydroxyl group, a suitable substituent, especially, one employable as an hydroxyl-protecting group, as exemplified by, besides alkoxy, alkenyloxy, aralkyloxy, acyloxy and aryloxy. Preferred examples of the alkoxy group include those having 1 to 10 carbon atoms (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy). As alkenyloxy, mention is made of those having 1 to 10 carbon atoms, including, for example, allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy and 2-cyclohexenylmethoxy, and, as aralkyloxy, mention is made of, for example, phenyl -(C_1-C_4)alkyloxy (e.g., benzyloxy and phenethyloxy). Preferred examples of acyloxy include alkanoyloxy having 2 to 4 carbon atoms (e.g., acetyloxy, propionyloxy, n-butyryloxy and isobutyryloxy). As aryloxy, mention is made of 4-chlorophenoxy, among others.

As the optionally substituted thiol group, mention is made of, besides the thioly group, such groups as have, on this thiol group, a suitable substituent, especially one employable as a thiol-protecting group, as exemplified by alkylthio, aralkylthio and acylthio. Preferred examples of alkylthio include alkylthio having 1 to 10 carbon atoms (.e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio and cyclohexylthio. As aralkylthio, mention is made of, for example, phenyl-(C_1-C_4)alkylthio (e.g., benylthio and phenthylthio). Preferred examples of acylthio include alkanoylthio having 2 to 4 carbon atoms (e.g., acetylthio, propionylthio, n-butyrylthio and iso-butyrylthio). As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl (e.g., a group having 2 to 5 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl), aralkyloxycarbonyl (e.g. benzyloxycarbonyl) and aryloxycarbonyl (e.g. phenoxycarbonyl and p-tolyoloxycarbonyl).

In the above-mentioned general formula (I), substituents on the hydrocarbon residue and heterocyclic group shown as R may, when they are an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group or a non-aromatic heterocyclic group, have one or more, preferably 1 to 3, suitable substituents, respectively. Examples of these substituents include lower alkyl groups having 1 to 4 carbon atoms, lower alkenyl groups having to 2 to 5 carbon atoms, lower alkynyl groups having 2 to 5 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, aryl groups (e.g., phenyl or naphthyl), aromatic heterocyclic groups (e.g., thienyl, funyl, pyridyl, oxazolyl or thiazolyl), non-aromatic heterocyclic groups, (e.g., tetrahydrofuryl, morpholino, piperidino, pyrrolidino or piperazino), aralkyl groups having 7 to 9 carbon atoms, the amino group, N-mono-(C_1-C_4)alkylamino groups, N,N-di(C_1-C_4)alkylamino groups, amidino groups, an acyl group having 2 to 5 carbon atoms, a carbamoyl group, N-mono(C_1-C_4)alkyl carbamoyl groups, an N,N-di(C_1-C_4)alkyl carbamoyl group, a sulfamoyl group, N-mono(C_1-C_4)alkyl sulfamoyl groups, N,N-di(C_1-C_4)alkylsulfamoyl groups, a carboxyl group, lower alkoxycarbonyl groups having 2 to 5 carbon atoms, an hydroxyl group, lower alkoxy groups having 1 to 4 carbon atoms, lower alkenyloxy groups having 2 to 5 carbon atoms, cycloalkyloxy groups having 3 to 7 carbon atoms, aralkyloxy groups having 7 to 9 carbon atoms, aryloxy groups (e.g., phenyloxy or naphthyloxy), a mercapto group, lower alkylthio groups having 1 to 4 carbon atoms, aralkylthio groups having 7 to 9 carbon atoms, arylthio groups (e.g., phenylthio or naphthylthio), a sulfo group, a cyano group, an azide group, a nitro group, a nitroso group and halogen (e.g., fluorine, chlorine, bromine or iodine).

In the above formula (I), when each of m and n is 0, carbon substituted by R^1 is directly bonded to R; when m is 0 and n is 1 or 2, R is directly bonded to -$(CH_2)_n$-; and, when m is 1 and n is 0, Y is directly bonded to the carbon substituted by R^1.

Y is -CO-, -CH(OH)- or -N(R^3)-, preferably, -CH(OH)- or -N(R^3)-. The alkyl group represented by R^3 has 1 to 4 carbon atoms, e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl. As the substituent of the alkyl, an halogen atom (e.g., fluorine, chlorine, bromine or iodine), an alkoxy group having 1 to 4 carbon atoms, (e.g., methoxy, ethoxy, propoxy, n-butoxy or t-butoxy), hydroxyl, nitro, an acyl group having 1 to 4 carbon atoms (e.g. formyl, acetyl or propionyl) are mentioned.

The bivalent straight or branched chain hydrocarbon residue shown as A includes saturated residues [e.g., - CH_2-, -$(CH_2)_2$-, -$CH(CH_3)$-, -$(CH_2)_3$-, -$CH(C_2H_5)$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$- and -$(CH_2)_7$-], and unsaturated ones (e.g., -CH=CH-, -$C(CH_3)$=CH-, -CH=CH-CH_2-, -$C(C_2H_5)$=CH-, -CH_2-CH=CH-CH_2-, -CH_2-CH_2-CH=CH-CH_2-, -CH=CH-CH=CH-CH_2- and -CH=CH-CH=CH-CH=CH-CH_2-.

In the formula (I-C8), the lower alkyl group shown as D has 1 to 4 carbon atoms e.g., methyl, ethyl, n-propyl, i-propyl or n-butyl.

The pharmaceutically acceptable salts of the compounds (I) of this invention are exemplified by pharmaceutically acceptable salts with an inorganic base, salts with an organic base, salts with an inorganic acid, salts with an organic acid, and salts with a basic or acidic amino acid. Preferred examples of pharmaceutically acceptable salts with an inorganic base include alkali metal salts such as sodium salts and potassium salts; al-

kaline earth metal salts such as calcium salts and magnesium salts; and aluminium salts, ammonium salts or the like. Preferred examples of pharmaceutically acceptable salts with an organic base include those with, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. Preferred examples of pharmaceutically acceptable salts with an inorganic acid include those with, for example, hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid or phosphoric acid. Preferred examples of pharmaceutically acceptable salts with an organic acid include those with, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. Preferred examples of pharmaceutically acceptable salts with a basic amino acid include those with, for example, arginine, hysine and ornithine, and preferred examples of pharmaceutically acceptable salts with an acidic amino acid include those with, for example, aspartic acid and glutamic acid.

Among the above, the sodium salt and the potassium salt are more preferred.

The compounds (I) and their pharmaceutically acceptable salts of the present invention display the action of lowering blood sugar with low toxicity, which can be used as such or in a composition with, for example, a per se known pharmaceutically acceptable carrier, excipient or filler as a therapeutic agent for diabetes in mammals, including man. The compounds (I) and their pharmaceutically acceptable salts of the present invention also exhibit an improved activity of insulin resistance and can also be used as a hypotensor.

The compounds (I) of this invention and their pharmaceutically acceptable salts are low in toxicity. For example, oral administration of the compound of Example 18 (below) at a dosage of 15 mg/kg/day for 4 days to mice caused no change in body weight and liver weight in comparison with the control group. Furthermore, oral administration of the compound produced in Example 18 at a dosage of 100 mg/kg, or intraperitoneal administration at a dosage of 50 mg/kg, did not kill any test animals.

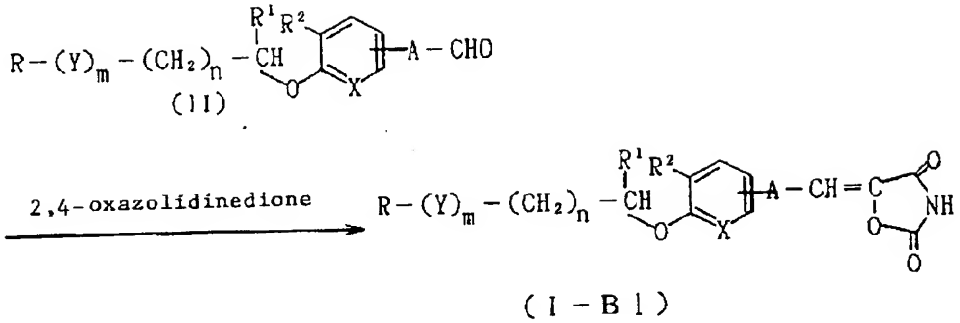
The administration is usually performed orally in the form of, for example, tablets, capsules (including soft capsules and microcapsules), powders and granules, and, depending on cases, non-orally in the form of, for example, injections, suppositories and pellets. The dosage for adults in the case of oral administration ranges from 0.05 to 10 mg/kg per day, desirably once to three times a day.

The compounds (I) and their pharmaceutically acceptable salts of this invention, mixed with pharmaceutically acceptable carriers, can be administered orally or non-orally in the form of solid preparations such as tablets, capsules, granules and powders; or in the form of liquid preparations such as syrups and injections.

As pharmaceutically acceptable carriers, use is made of conventional organic or inorganic carriers for pharmaceutical preparations, more specifically, for example, excipients, lubricants, binders and disintegrators for solid preparations; and solvents, solubilizers, suspending agents, isotonizers, buffering agents and local anaesthetic agents. Where required, such additives as antiseptics, anti-oxidants, colorants and sweeteners are further used. Preferred examples of pharmaceutically acceptable excipients include lactose, sucrose, D-mannitol, starch, crystalline cellulose and light silicon dioxide. Preferred examples of pharmaceutically acceptable lubricants include magnesium stearate, calcium stearate, talc and colloidal silica. Preferred examples of pharmaceutically acceptable binders include crystalline cellulose, sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and polyvinyl pyrrolidone. Preferred examples of pharmaceutically acceptable disintegrators include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, crosscarmelose sodium and carboxymethyl starch sodium. Preferred examples of pharmaceutically acceptable solvents include distilled water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil. Preferred examples of pharmaceutically acceptable solubilizers include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-amino methane, cholesterol, triethanolamine, sodium carbonate and sodium citrate. Preferred examples of pharmaceutically acceptable suspending agents include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerin monostearate; and hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose. Preferred examples of pharmaceutically acceptable isotonizers include sodium chloride, glycerin and D-mannitol. Preferred examples of pharmaceutically acceptable buffering agents include buffer solutions of phosphates, acetates, carbonates and citrates. Preferred examples of pharmaceutically acceptable local anaesthetic agents include benzyl alcohol. Preferred examples of pharmaceutically acceptable antiseptics include paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid. Preferred examples of pharmaceutically acceptable anti-oxidants include sulfites and ascorbic acid.

The following is a description of methods of producing the compounds (I) of this invention and their pharmaceutically acceptable salts.

Method A



(II)

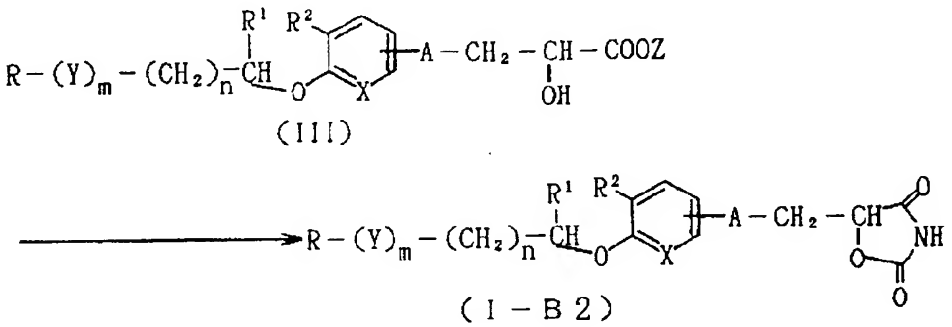
(I-B1)

[wherein each symbol has the same meaning as defined above].

The compound (I-B1) can be produced by condensation of the compound (II) with 2,4-oxazolidinedione. This reaction is conducted in a solvent in the presence of a base. As the solvent, mention is made of alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; N,N-dimethylformamide, dimethyl sulfoxide and acetic acid. As the base, use is made of sodium alkoxide (e.g. sodium methoxide or sodium ethoxide), potassium carbonate, sodium carbonate, sodium hydride, sodium acetate or a secondary amine such as piperidine, piperazine, pyrrolidine, morpholine, diethylamine or diisopropylamine, among others. The amount of 2,4-oxazolidinedione to be used ranges from 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents, relative to the compound (II). The amount of the base to be used ranges from 0.01 to 5 molar equivalents, preferably 0.05 to 2 molar equivalents, relative to the compound (II). This reaction is conducted at temperatures ranging from 0 to 150°C, preferably from 20 to 100°C, over a period ranging from 0.5 to 30 hours.

The compound (I-B1) to be produced by the above method is, in some instances, obtained as a mixture of (E) - compound and (Z) - compound, relative to the double bond at the 5-position of the 2,4-oxazolidinedione ring.

Method B



(III)

(I-B2)

(wherein Z is hydrogen, a lower alkyl group having 1 to 4 carbon atoms or an aralkyl group, and the other symbols have the meanings given above).

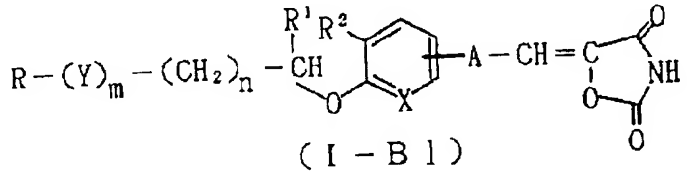
In the above-mentioned general formula (III), the "lower alkyl" group shown as Z, having 1 to 4 carbon atoms, may be, e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl). By the aralkyl group shown as Z is meant an alkyl group having an aryl group as a substituent thereon. Examples of the aryl groups include phenyl and naphthyl, which may optionally be substituted with the afore-mentioned alkyl groups having 1 to 4 carbon atoms, halogen atoms (e.g. fluorine, chlorine, bromine or iodine), the hydroxyl group or the nitro group. As the alkyl moiety of the aralkyl group, alkyls having 1 to 4 carbon atoms, such as methyl, ethyl or propyl may be mentioned. Preferred examples of the aralkyl group include benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-naphthyl)methyl. Among them, benzyl and phenethyl are most preferred.

An alkali metal salt of the compound (I-B2) can be produced by allowing a compound (III) to react with an

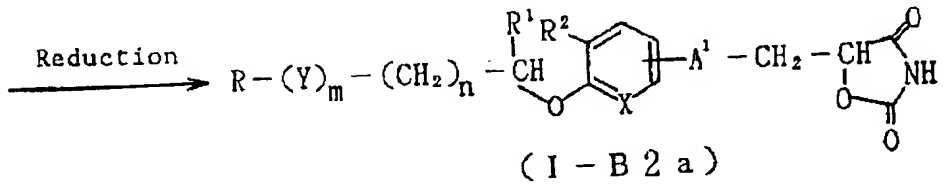
alkali metal cyanate such as potassium cyanate or sodium cyanate. Then, the alkali metal salt is treated with an acid to produce the compound (I-B2). The reaction of the compound (III) with the alkali metal cyanate is conducted in an adequate solvent. As the solvent, use is generally made of alcohols such as methanol, ethanol, propanol, isopropanol, 2-methoxyethanol and butanol, N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, or a suitable mixture thereof. The amount of the alkali metal cyanate to be used ranges from 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents. The reaction temperature ranges from 0 to 150°C, preferably from 10 to 120°C, and the reaction time ranges from 0.5 to 50 hours. The alkali metal salt of the compound (I-B2) thus obtained is treated with an acid by conventional means to produce the compound (I-B2). This acid treatment is conducted in the presence or the absence of a suitable solvent. Examples of a suitable solvent include alcohols such as methanol, ethanol, propanol, isopropanol, 2-methoxyethanol and butanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane; ethyl acetate, acetonitrile, or mixtures of such solvents. As the acid, use is preferably made of an excess amount of an inorganic acid such as hydrochloric acid, sulfuric acid, nitric acid or hydrobromic acid, while an organic acid such as acetic acid, citric acid, tartaric acid or the like can also be used.

The resulting 2,4-oxazolidinedione derivative (I-B2) can be isolated and purified by a known isolating and purifying means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography or the like.

Method C



(I-B1)



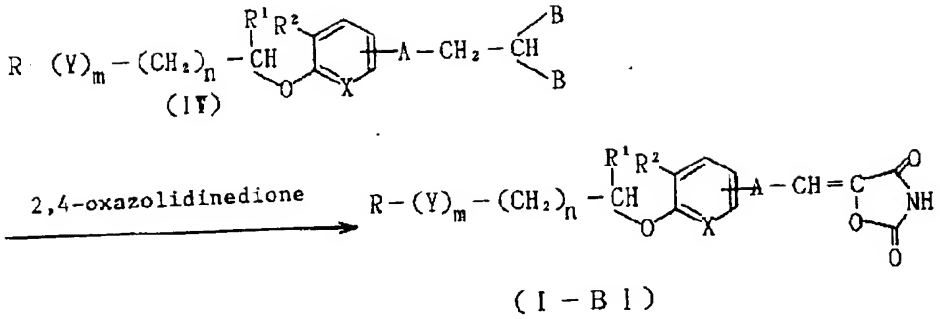
(I-B2a)

[wherein A^1 is a saturated bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms, and the other symbols have the meanings given above].

The saturated bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atom shown as A is the saturated residue having the meaning given above for A.

By subjecting the compound (I-B1) to reduction, the compound (I-B2a) can be produced. This reduction is conducted, in accordance with a conventional method, in the presence of a catalyst under an hydrogen atmosphere of 1 to 150 atmospheric pressures. As the solvent, mention is made of alcohols such as methanol, ethanol, propanol, isopropanol or 2-methoxyethanol, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as ethyl ether, isopropyl ether, dioxane or tetrahydrofuran, halogenated hydrocabons such as chloroform, dichloromethane or 1,1,2,2-tetrachloroethane, ethyl acetate, acetic acid, N,N-dimethylformamide, or a suitable mixture of such solvents. Examples of preferred catalysts include metals such as nickel compounds and transition metals such as palladium, platinum and rhodium. Reaction temperatures range from 0 to 100°C, preferably from 10 to 80°C. Reaction times range from 0.5 to 50 hours. The 2,4-oxazolidinedione derivative (I-B2a) thus obtained can be isolated and purified by a known refining means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer or chromatography.

Method D



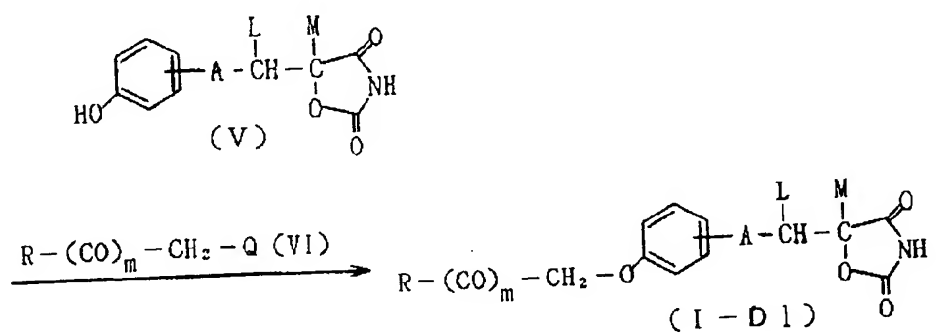
(I-B1)

[wherein B stands for lower (C_1-C_4) alkoxy, lower (C_1-C_4) alkylthio or lower (C_1-C_4) acyloxy; and the other symbols have the same meaning as given above].

As the lower (C_1-C_4) alkoxy, lower (C_1-C_4) alkylthio and lower (C_1-C_4) acyloxy, respectively shown as B, mention is made, respectively, of alkoxy groups having 1 to 4 carbon atoms such as, for example, methoxy, ethoxy propoxy, isopropoxy and butoxy; alkylthio groups having 1 to 4 carbon atoms such as, e.g., methylthio, ethylthio, propylthio, i-propylthio and butylthio; and acyl groups having 1 to 4 carbon atoms such as, e.g., acetyloxy or propionyloxy. Depending on the case, two B groups may be combined with each other to form, for example, ethylenedioxy, propylenedioxy or dithiotrimethylene. In other words, by the $-CH(B)_2$ moiety in formula (IV) is meant a protected aldehyde group.

The compound (IV) is condensed with 2,4-oxazolidinedione to produce a compound (I-B1). This condensation reaction is conducted in substantially the same manner as in the reaction of the compound (II) with 2,4-oxazolidinedione in Method A.

Method E



(I-D1)

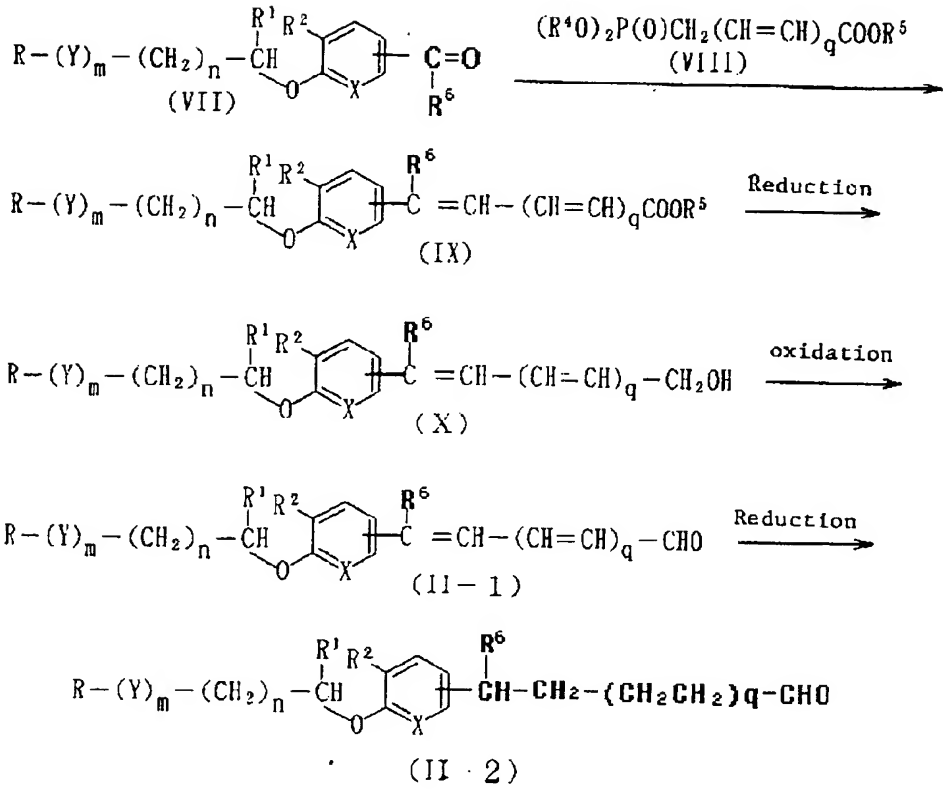
[wherein Q is a leaving group and the other symbols have the same meaning as given above].

As the leaving group shown as Q, mention is made, e.g., of an halogen (e.g. chlorine, bromine or iodine), methanesulfonyloxy, benzenesulfonyloxy and p-toluenesulfonyloxy.

The compound (V) is condensed with the compound (VI) to produce a compound (I-DI). This reaction is conducted, in accordance with a conventional method, in an adequate solvent in the presence of a base. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; ketones such as acetone and 2-butanone; N,N-dimethylformamide, dimethylsulfoxide, chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; and suitable mixtures of these solvents. As the base, mention is made of an alkali metal salt, such as sodium hydroxide, potassium hydroxide, potassium carbonate and sodium hydrogencarbonate; amines such as pyridine, triethylamine and N,N-dimethylaniline; metal hydroxides such as sodium hydroxide and potassium hydroxide; sodium ethoxide, sodium methoxide and potassium t-butoxide, among others. The amount of these bases to be used is preferably in a range of from 1 to 5 mol. relative to the compound (V). This reaction is conducted usually at temperatures ranging from -50°C to 150°C, preferably from -10°C to 100°C. The reaction time ranges from 0.5 to 30 hours.

The starting compound of Method A can, for example, be prepared by Method F.

Method F



[wherein R^4 and R^5 independently stand for a lower (C_1-C_4) alkyl group; R^6 stands for hydrogen or a lower (C_1-C_4) alkyl group; q denotes 0, 1 or 2; and the other symbols have the same meaning as defined above].

Examples of the lower (C_1-C_4) alkyl groups shown as R^4, R^5 and R^6 include methyl, ethyl, propyl, isopropyl and butyl.

In this method, first, a formyl or an acyl derivative (VII) is allowed to react with a phosphonoacetic acid derivative or an ω-phosphonocarboxylic acid derivative (VIII) to produce an unsaturated ester derivative (IX). The reaction of (VII) with (VIII) is conducted, in accordance with a conventional method, in an adequate solvent in the presence of a base. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol and propanol; N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tretrachloroethane, as well as a suitable mixture of these solvents. Examples of the base include alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; amines such as pyridine, triethylamine and N,N-dimethyl aniline; metal hydrides such as sodium hydride and potassium hydride; sodium ethoxide, sodium methoxide and potassium t-butoxide. The amount of these bases to be employed ranges, preferably, from 1 to 5 mol. relative to the compound (VIII). The amount of the compound (VIII) to be used ranges from 1 to 5 mol., preferably from 1 to 3 mol., relative to the compound (VII). This reaction is conducted generally at temperatures ranging from -50°C to 150°C, preferably from about -10°C to 100°C. The reaction time ranges from 0.5 to 30 hours.

The compound (IX) is then subjected to reduction to produce an alcohol derivative (X). This reduction reaction can be conducted by a per se known method, for example, reduction with a metal hydride, reduction with a metal hydride complex, or reduction with diborane and a substituted borane. In other words, this reaction can be conducted by treating the compound (IX) with a reducing agent. Examples of the reducing agent include alkali metal borohydrides (e.g. sodium borohydride or lithium borohydride); metal hydride complexes such as lithium aluminum hydride: and diborane, and the use of diisobutyl aluminum hydride serves to further the reaction advantageously. This reaction is conducted in an organic solvent inert to the reaction. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; ethers such as diethyl ether, tetrahydrofuran and dioxane; alcohols such as methanol, ethanol, propanol, iso-

propanol and 2-methoxyethanol; amides such as N,N-dimethylformamide; or a suitable mixture of these solvents, and, from among these solvents, a suitable one is selectively employed depending on the kind of reducing agent used. The reaction temperature ranges from -20°C to 150°C, especially preferably from 0°C to 100°C, and the reaction time ranges from 1 to 24 hours.

Then, the compound (X) is subjected to oxidation to produce an unsaturated aldehyde derivative (II-1). This oxidation reaction can be conducted by a per se known method, for example, oxidation with manganese dioxide, oxidation with chromic acid, oxidation with dimethyl sulfoxide, or the like. In other words, the reaction is conducted by processing the compound (X) with an oxidizing agent. As the oxidizing agent, use is made of manganese dioxide or chromic anhydride; use of the former is preferred to conduct the reaction more advantageously. This reaction is conducted in an organic solvent inert to the reaction. As the solvent, use is made of, for example, aromatic hydrocarbons such as benzene, toluene or xylene, halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane or 1,1,2,2-tetrachloroethane, ethers such as diethyl ether, tetrahydrofuran or dioxane, dimethyl sulfoxide or a suitable mixture solvent thereof, and, from among these solvents, a suitable one is selectively employed depending on the kind of oxidizing agent used. The reaction temperatures range from -20°C to 150°C, those ranging from 0°C to 100°C being preferred, and the reaction time ranges from 1 to 24 hours.

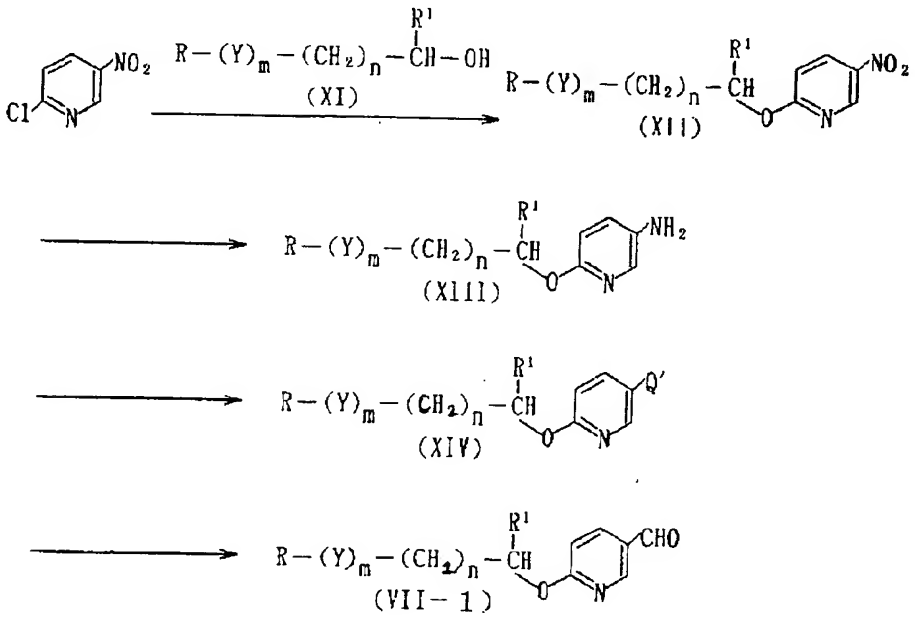
Then, the compound (II-1) is subjected to a reduction reaction to produce the compound (II-2). This reduction reaction is conducted in the same manner as Method C.

The aldehyde derivative (II-1), (II-2) thus obtained can be isolated and purified by means of a conventional refining process, for example, concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography or the like.

The compound (VII), which is the starting compound in Method F, can be synthesized in accordance with any of the methods described in, for example, Chemical & Pharmaceutical Bulletin, Vol.39, p.1440 (1990), JPA H4(1992)-225978, JPA S61(1986)-85372, JPA S61(1986)-271287, JPA S63(1988)-139182, JPA H3(1991)-170478, WO9119496-Al, EP-428312-A, JPA HI(1989)-299289 and JPA S63(1988)-230689.

The pyridine aldehyde derivatives (VII-1) can, for example, be prepared by Method G.

Method G



[wherein Q' is an halogen atom, and the other symbols have the meanings given above].

As the halogen atom shown as Q', chlorine, bromine and iodine may be mentioned.

In this method, firstly, 2-chloro-5-nitropyridine is allowed to react with an alcohol derivative to yield the compound (XII). The reaction of 2-chloro-4-nitropyridine with the compound (XI) is conducted in a suitable solvent in the presence of a base in accordance with a conventional method. As the solvent, mention is made of, for example, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as dioxane, tetrahydro-

furan or dimethoxyethane, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, or a suitable mixture solvent thereof. As the base, mention is made of alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate or sodium hydrogencarbonate; amines such as pyridine, triethylamine or N,N-dimethylaniline; metal hydrides such as sodium hydride or potassium hydride; sodium ethoxide, sodium methoxide and potassium t-butoxide. The amount of these bases to be used is preferably in the range from 1 to 5 mol. relative to the compound (XI). This reaction is conducted usually at temperatures ranging from -50°C to 150°C, preferably from -10°C to 100°C. The reaction time ranges from 0.5 to 30 hours.

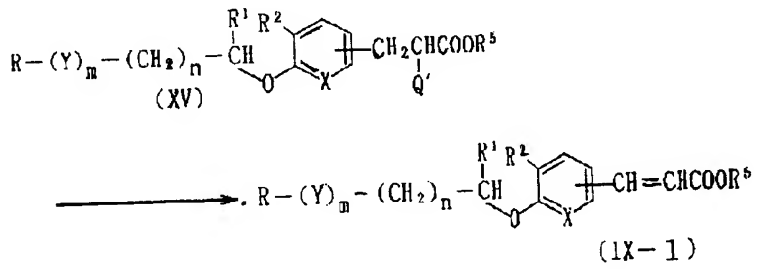
Then, the compound (XII) is subjected to reduction to produce an amine derivative (XIII). While the reduction reaction can be conducted by a per se known method, catalytic reduction using a metal catalyst serves to perform the reduction more advantageously. This catalytic reduction is conducted, in accordance with a conventional method, in the presence of a catalyst in an hydrogen atmosphere of 1 to 150 atmospheric pressures. Examples of the solvent include alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as ethyl ether, isopropyl ether, dioxane and tetrahydrofuran; halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane; ethyl acetate, acetic acid, N,N-dimethylformamide, or a suitable mixture solvent thereof. Use of, for example, a metal such as a nickel compound or a transition metal catalyst such as palladium, platinum or rhodium as the catalyst leads to advantageous performance of the reaction. The reaction temperature ranges from 0 to 100°C, preferably from 10 to 80°C, and the reaction time ranges from 0.5 to 50 hours.

Then, the compound (XIII) is subjected to the per se known Sandmeyer reaction to yield an halogen derivative (XIV). In this reaction, firstly, the compound (XIII) is diazotized by adding dropwise thereto an aqueous solution of sodium nitrite in a solvent in the presence of hydrochloric acid, hydrobromic acid or hydroiodic acid. The diazotized compound being then allowed to react with an aqueous solution of sodium halogenate or potassium halogenate, so as thereby to produce the compound (XIV). As the solvent, use is made of alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; ethers such as acetone, 2-butanone, dioxane and tetrahydrofuran; or a suitable mixture solvent thereof. The reaction temperature ranges from -50°C to 100°C, preferably from -20 to 60°C. The reaction time ranges from 0.5 to 50 hours.

Then, the compound (XIV) is processed with, for example, butyl lithium, sec.-butyl lithium, tert.-butyl lithium, methyl lithium, phenyl lithium or phenyl magnesium bromide, which is then allowed to react with N,N-dimethylformamide (DMF) to produce a compound (VII-1).

A part of the intermediate compound (IX) in Method F can be produced also by, for example, Method H.

Method H



(XV)

(IX-1)

[wherein each symbol has the same meaning as given above].

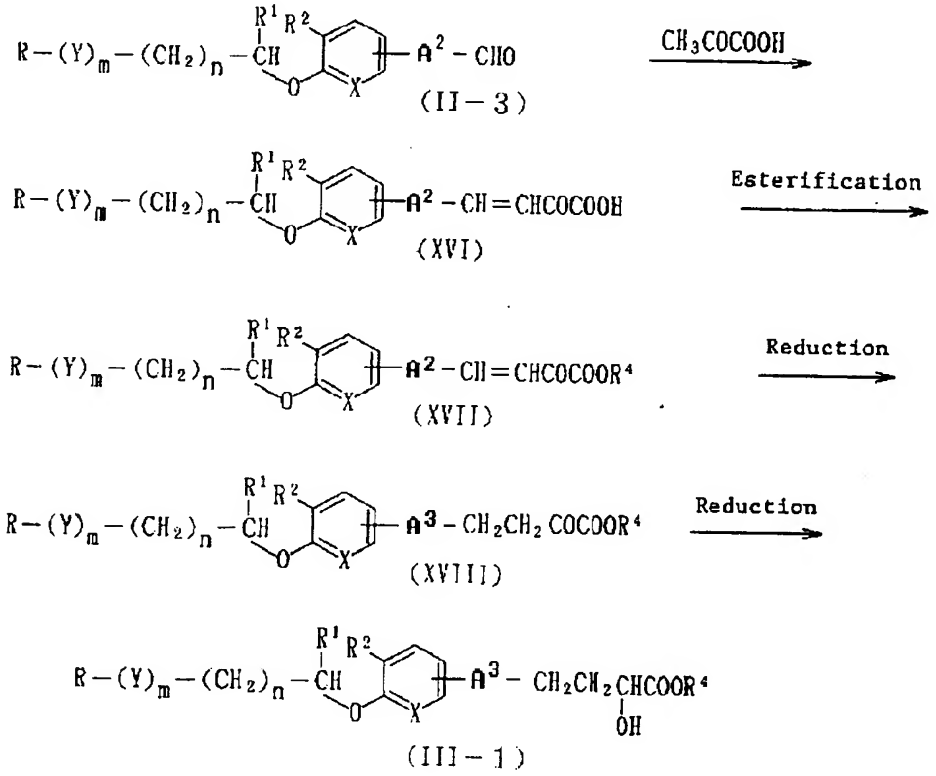
This reaction can be conducted in a suitable solvent in the presence of a base. As the solvent, mention is made of aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol and propanol; ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanone, and a suitable mixture solvent of them. As the base, mention is made of an inorganic base, including, for example, an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide), an alkaline earth metal hydroxide (e.g. magnesium hydroxide or calcium hydroxide), an alkali metal carbonate (e.g. sodium carbonate or potassium carbonate), an alkaline earth metal carbonate (e.g. magnesium carbonate or calcium carbonate), an alkali metal hydrogencarbonate (e.g. sodium hydrogencarbonate or potassium hydrogencarbonate) and an alkali metal acetate (e.g. sodium acetate or potassium acetate); and an organic base including trialkylamine (e.g. trimethylamine or triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo [4,3,0] non-5-ene, 1,4-diazabicyclo [2,2,2] non-5-ene and 1,8-diazabicyclo [5,4,0]-7-un-

decene. The amount of these bases to be used ranges preferably from 1 to 5 mol. relative to the compound (XV). This reaction is conducted usually at temperatures ranging from -20°C to 150°C, preferably from -10°C to 100°C.

Methods of synthesizing the starting compound (XV) in Method H are described in, for example, Chemical & Pharmaceutical Bulletin, 30, p.3563 (1982), Chemical & Pharmaceutical Bulletin, 30, p.3580 (1982), Chemical & Pharmaceutical Bulletin, 32, p.2267 (1984), Arzneimittel-Forschung/Drug Research 40, p37 (1990), Journal of Medicinal Chemistry, 35 p.2617 (1992), JPA S61(1986)-267580, JPA S61(1986)-286376, JPA S61(1986)-85372, JPA H2(1990)-31079 and JPA S62(1987)-5981.

The compound (III) used in Method B is produced by, for example, Method I.

Method I



[wherein A^2 is a bond or a bivalent straight or branched chain hydrocarbon residue having 1 to 5 carbon atoms; A^3 is a bond or a bivalent saturated straight or branched chain hydrocarbon residue having 1 to 5 carbon atoms, and the other symbols have the same meaning as given above].

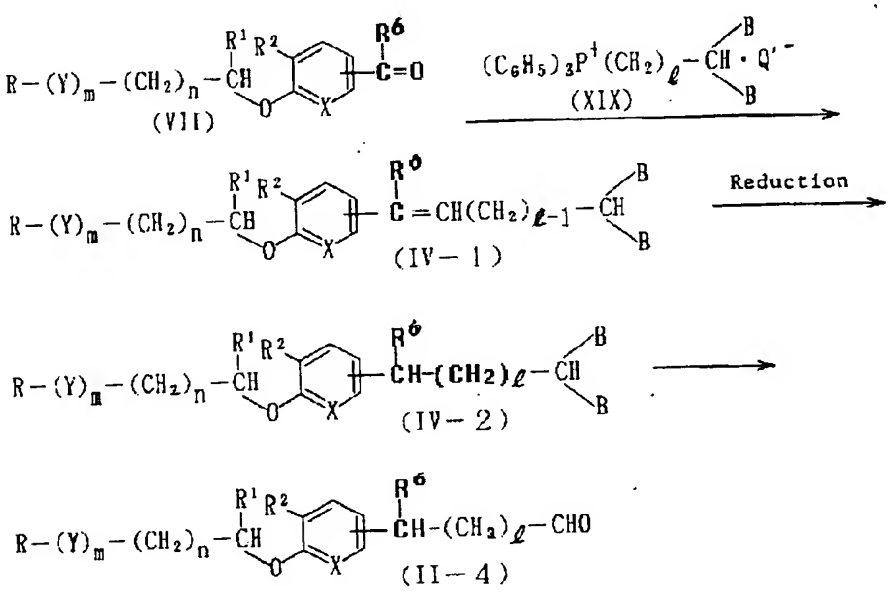
The bivalent straight or branched chain hydrocarbon residue shown as A^2 is a residue having 1 to 5 carbon atoms chosen among the bivalent straight or branched chain hydrocarbon residues shown as A, and the bivalent saturated straight or branched chain hydrocarbon residue shown as A^3 is a saturated residue chosen among the bivalent straight or branched chain hydrocarbon residues shown as A^2.

In this method, firstly, the compound (II-3) is condensed with pyruvic acid to produce a compound (XVI). The condensation reaction of the compound (II-3) with pyruvic acid is conducted in a mixture of alcohols and water using the same base as in the reaction of the compound (II) with 2,4-oxazolidinedione in Method A. The compound (XVI) is then subjected to esterification to produce a compound (XVII). The esterification reaction can be conducted by a per se known method, for example, a method which comprises allowing the compound (XVII) to react directly with an alcohol (R^4 OH) in the presence of an acid to cause esterification, or a method which comprises using a reactive derivative of the compound (XVI), for example, an acid anhydride, an acid halide (acid chloride or acid bromide), an imidazolide or a mixed acid anhydride (e.g. an anhydride with methyl carbonate, an anhydride with ethyl carbonate, an anhydride with isobutyl carbonate or the like) to adequately react with the alcohol (R^4OH). The compound (XVII) is then subjected to catalytic reduction to yield a compound (XVIII). This catalytic reduction is conducted in substantially the same manner as in Method C. The compound

(XVIII) is then subjected to reduction to yield a compound (III-1). This reduction reaction can be conducted by a per se known method. For example, reduction by using a metal hydride, reduction by using a metal hydride complex compound, reduction by using diborane or a substituted diborane, catalytic hydrogenation or the like are mentioned. In other words, this reaction is conducted by processing the compound (XVIII) with a reducing agent. As the reducing agent, mention may be made of an alkali metal borohydride (e.g. sodium borohydride or lithium borohydride), a metal hydride complex compound such as lithium aluminum hydride, a metal hydride such as sodium hydride, an organotin compound (e.g., triphenyltin hydride), metals and metal salts, including nickel compounds, zinc compounds or the like, transition metal catalysts including palladium, platinum, rhodium or the like, to be used together with hydrogen, and diborane, among others. Above all, use of an alkali metal borohydride (e.g., sodium borohydride or lithium borohydride) is advantageous. This reaction is conducted in an organic solvent which does not have an undesirable influence on the reaction. Examples of a suitable solvent include aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; ethers such as diethyl ether, tetrahydrofuran and dioxane; alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; amides such as N,N-dimethylformamide; or a suitable mixture of these solvents. From among these possibilities, a suitable solvent or solvent mixture is selectively employed depending on the type of reducing agent used. The reaction temperature ranges preferably from -20°C to 150°C, especially from 0°C to 100°C. The reaction time ranges from 1 to 24 hours.

The starting compound (IV) of Method D and the starting compound (II) of Method A may, for example, be prepared by Method J.

Method J

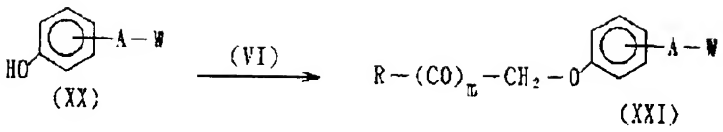


[wherein ℓ is an integer of from 1 to 6, and the other symbols have the meanings given above].

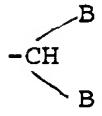
In this method, firstly, the compound (VII) is condensed with the compound (XIX) to yield a compound (IV-1). This condensation reaction is conducted in substantially the same manner as in the reaction of the compound (VII) with the compound (VIII) of Method F. The compound (IV-1) is then subjected to a reduction reaction to yield (IV-2). This reduction reaction is conducted in substantially the same manner as the catalytic reduction reaction of the compound (I-B1) in Method C. The compound (IV-2) may be converted to an aldehyde derivative (II-4) by subjecting the former to deprotection by processing with an acid in an aqueous solvent. As the aqueous solvent, mention may be made of a mixture with water of an alcohol such as methanol, ethanol or propanol; an ether such as tetrahydrofuran or dioxane; acetonitrile, acetone, 2-butanone, acetic acid or the like. As the acid, mention may be made of, for example, p-toluenesulfonic acid, apart from inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid or hydrobromic acid.

A part of the compounds (II) and (IV) can be prepared by Method K.

Method K



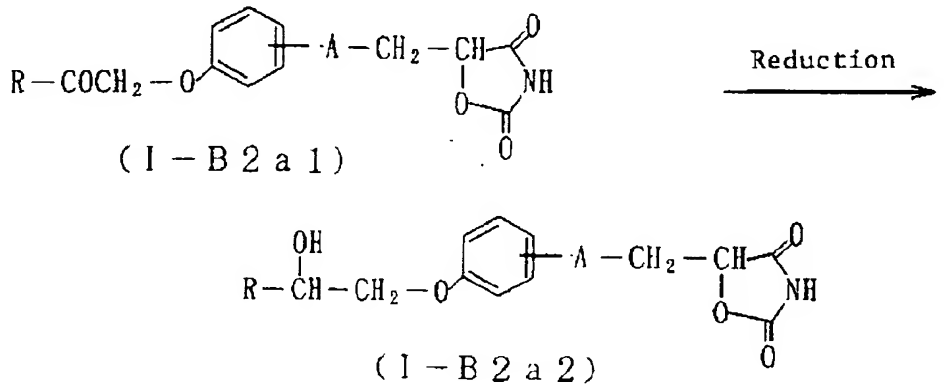
[wherein W is



(B has the meaning given above), and the other symbols have the meanings given above]. This reaction is carried out in a similar manner to that of Method E.

A part of the compound produced by Method E can be subjected to reduction to yield a compound (I-B2a2).

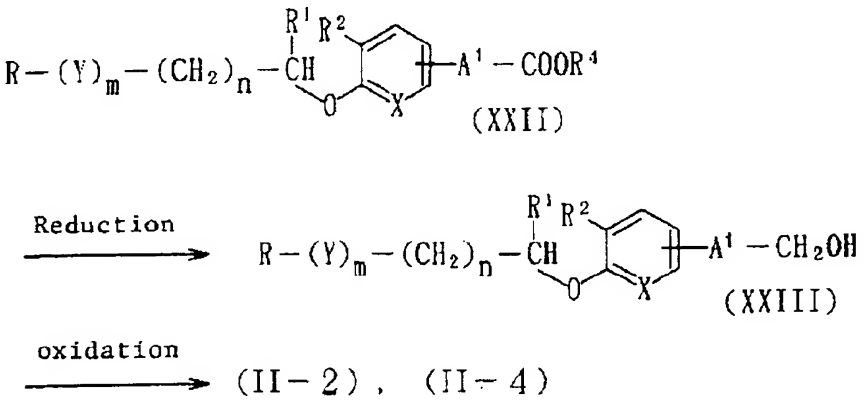
Method L



(wherein each symbol has the meaning given above.) This reaction is carried out in a similar manner to the reduction reaction of Method I in which compound (XVIII) is converted to compound (III-1).

The compounds (II-2) and (II-4) may also be prepared by Method M.

Method M



(wherein each symbol has the meaning given above.)

The compound (XXII), which is produced by catalytic hydrogenation of the compound (XI), can be converted to compound (XXIII). The reaction is carried out in a similar manner to that described in connection with the reaction of Method F in which the compound (IX) is converted to compound (X). Compound (XXIII) can be subjected to oxidation to yield compounds (II-2) and (II-4).

The oxidation reaction is carried out by a known conventional reaction such as, e.g., Jones's oxidation using sulfuric acid-pyridine, Collins's oxidation using a chromium oxide-pyridine complex, oxidation using pyridinium chlorochromate (PCC), or pyridinium dichromate (PDC), oxidation using activated dimethyl sulfoxide (DMSO) or oxidation using an oxoammonium salt. It is preferable to use activated DMSO when the the starting compound which is subjected to oxidation is optically active. Oxidation using activated DMSO is carried out in the presence of DMSO and an electrophilic reagent in a solvent. As the solvent, mention may be made of ethers (e.g. ethyl ether, isopropyl ether, tetrahydrofuran or dioxane), aromatic hydrocarbons (e.g. benzene, toluene or xylene), N,N-dimethylformamide (DMF), halogenated hydrocarbons (e.g. chloroform or dichloromethane), pyridine and dimethyl sulfoxide. From these solvents, a proper solvent can be selected in view of the kind of electrophilic reagent used.

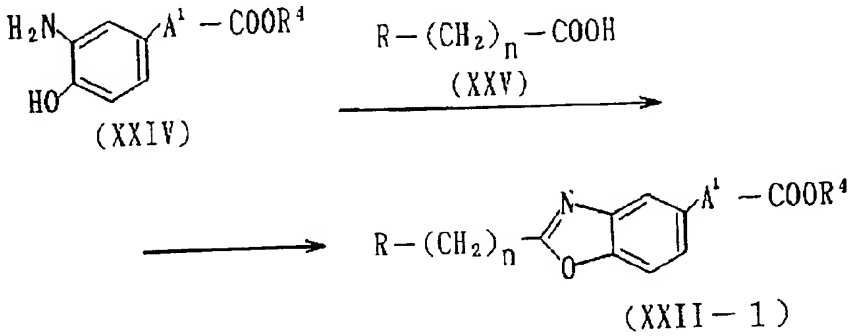
As the oxidation using DMSO, there are, for example, a dicyclohexylcarbodiimide-method, an acetic anhydride-method, a phosphorus pentoxide-method, a chlorine-method, a sulfur trioxide-pyridine-method, a keteneimine-enamine-method or a mercury-acetate (II)-method. Among them, the sulfur trioxide-pyridine-method is most advantageously used. The sulfur trioxide-pyridine-method is carried out by using a sulfur trioxide-pyridine complex as an activator for DMSO in the presence of triethylamine. This method can be carried out using an excess amount of DMSO as a solvent. Triethylamine and sulfur trioxide-pyridine complex are each used in the range of 1 to 10 mol equivalents, preferably 2 to 5 mol equivalents, relatively to one mole equivalent of the compound (XXIII). The reaction temperature is -70°C to 80°C, preferably -20°C to 40°C. The reaction time ranges usually from 0.5 to 10 hours.

The aldehyde derivatives (II-2), (II-4) thus obtained may be isolated and purified by means of conventional refining processes, for example, concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography or the like.

The compounds (II-2) and (II-4) may be converted to the compound (IV-2) by acetalization or dithioacetalization.

Among the compounds (XXII), a benzoxazole derivative (XXII-1) can be prepared by Method N.

Method N



(wherein each symbol has the meaning given above)

The reaction is conducted in an organic solvent inert to the reaction. Examples of such solvent include aromatic hydrocarbons such as xylene, toluene or benzene, ethers such as tetrahydrofuran or dioxane and halogenated hydrocarbons such as dichlorobenzene, chlorobenzene or methylene chloride. While a sole solvent may be used, a mixture of two or more solvents may also be used.

The reaction is usually carried out by heating a mixture of compounds (XXIV) and (XXV) in a suitable solvent. The temperature is usually in the range of from 30°C to 200°C, preferably in the range of from 50°C to 180°C.

The reaction may be conducted in the presence of a dehydrating agent. As the dehydrating agent, a phosphorus compound such as phosphorus pentoxide or phosphorus oxychloride may be mentioned. The dehydrating agent is used in an amount of from 1 to 10 mole equivalents, preferably 1 to 4 mole equivalents relative

to the compound (XXIV). When phosphorus oxychloride is used, it can be used in a large excess as a solvent. When phosphorus pentoxide is used, the addition of hexamethyldisiloxane $\{[CH_3)_3Si]_20\}$ is advantageous to facilitate the reaction. In this case, it is preferable to use hexamethyldisiloxane in an amount of 2 to 4 mole equivalents relative to the phosphorus pentoxide. The reaction time is usually 1 to 30 hours, preferably 1 to 10 hours.

The compounds (I) of the invention prepared by the methods described above can, if desired, be converted to pharmaceutically acceptable salts thereof by conventional methods known per se.

The compounds (I) of this invention and their pharmaceutically active salts possess excellent hypoglycemic and hypolipidemic activities.

Experimental Example

Hypoglycemic and hypolipidemic actions in mice

A test compound mixed in a powdery feed (CE-2, Japan Clea) at a rate of 0.005% was fed to KKA^Y mice (9-14 weeks old) freely for 4 days. During that period, the animals had free access to water. Blood was collected from the orbital venous plexus. Using the plasma, glucose and triglyceride were enzymatically quantitatively determined using an Iatrochem-GLU(A) and an Iatro-MA701 TG kit (Iatron Inc.). The respective values are percentage reductions (%) found in drug-dosed groups from the control group not receiving the test compound, as shown in [Table 1], just below.

Table 1

Compound (Example No.)	Hypoglycemic Action % reduction	Hypolipidemic Action % reduction
18	49	41
19	50	36
23	39	33
24	56	53
26	42	32
27	53	15
29	61	83
30	57	70
32	63	60
33	45	59
34	43	51
35	42	32
36	56	48
43	58	75
52	54	82

Table 1 (continued)

Compound (Example No.)	Hypoglycemic Action % reduction	Hypolipidemic Action % reduction
56	32	24
60	54	77

As stated above, 2,4-oxazolidinedione derivatives (I) of the present invention exhibit excellent hypoglycemic and hypolipidemic actions, and are pharmaceutically useful as therapeutic agents for diabetes, hyperlipemia and hypertension, for example.

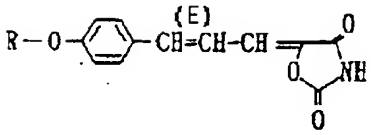
Example 1

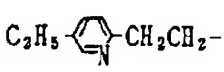
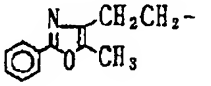
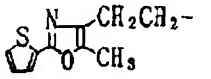
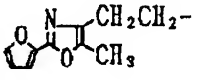
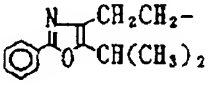
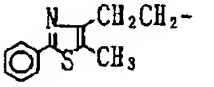
A mixture of (E)-4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]cinnamaldehyde (1.20g), 2,4-oxazolidinedione (0.525 g), piperidine (0.09 g) and ethanol (20 ml) was heated for 5 hours under reflux. The reaction mixture was poured into water, which was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried (MgS04) and, then, concentrated. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with chloroform-methanol (50:1) was obtained 5-[4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]cinnamylidene]-2,4-oxazolidinedione (0.51g, 34%). Recrystallization from dichloromethane-methanol gave pale yellow prisms, m.p.213-214°C.

Examples 2 to 7

In substantially the same manner as in Example 1, the compounds shown in Table 2 (below) were obtained.

[Table 2]



Example No.	R	Yield (%)	m.p. (℃)	Recrystallization solvent
2		30	211-213 (decomposition)	chloroform-methanol
3		26	227-228	chloroform-methanol
4		29	222-224	dichloromethane-methanol
5		31	206-207	dichloromethane-methanol
6		23	Note 1) 197-198	chloroform-methanol-hexane
7		23	203-204	ethyl acetate - hexane

Note 1) 1/2 hydrate

Example 8

In substantially the same manner as in Example 1, 5-[3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]-2-propenylidene]-2,4-oxazolidinedione was obtained. Recrystallization from ethanol - chloroform - isopropyl ether gave pale yellow crystals, m.p.204-205°C.

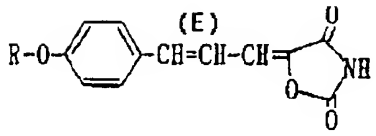
Example 9

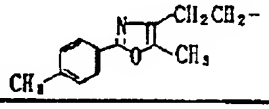
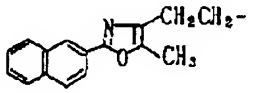
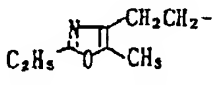
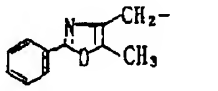
A mixture of 2-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propyl]-1,3-dioxane (2.0 g), 2,4-oxazolidinedione (0.99 g), piperidine (0.21 g) and acetic acid (50 ml) was heated for 24 hours under reflux. The reaction mixture was concentrated under reduced pressure, to which was added ethyl acetate. The ethyl acetate layer was washed with an aqueous solution of sodium hydrogencarbonate, 2N HCl and water, successively, which was then dried ($MgSO_4$), followed by concentration. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with chloroform - ethyl acetate (5:1), 5-[4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butylidene]-2,4-oxazolidinedione (0.55 g, 26%) was obtained. Recrystallization from ethyl ether - methanol gave colorless needles, m.p.152-153°C.

Example 10 to Example 13

In substantially the same manner as in Example 1, compounds shown in [Table 3] were obtained.

[Table 3]



Example No.	R	Yield (%)	m.p. (℃)	Recrystallization solvent
10		33	198-200	dichloromethane methanol
11		31	195-197	dichloromethane methanol
12		42	201-203	methanol-ethyl acetate
13		26	244-245	chloroform-methanol

Example 14

In substantially the same manner as in Example 1, (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-yl]acrolein was allowed to react with 2,4-oxazolidinedione to give 5-[3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-yl]-2-propenylidene]-2,4-oxazolidinedione. The yield was 44%. Recrystallization from dichloromethane-methanol gave pale yellow needles, m.p.237-239°C.

Example 15

In substantially the same manner as in Example 1, (E,E)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4-pentadien-1-al was allowed to react with 2,4-oxazolidinedione to give 5-[5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4-pentadienylidene]-2,4-oxazolidinedione. The yield was 31%. Recrystallization from dichloromethane-methanol gave yellow needles, m.p.209-211°C.

Example 16

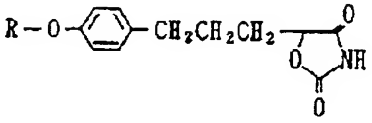
A mixture of 5-[4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]cinnamylidene]-2,4-oxazolidinedione (0.29 g), palladium-carbon (10%, 0.1 g) and dioxane (50 ml) was subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with chloroform-methanol (100:3) was obtained 5-[3-[4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.28 g, 96%). This product was recrystallized from dichloromethane-methanol to give colorless prisms, m.p.149-150°C.

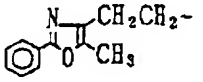
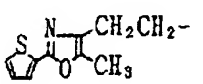
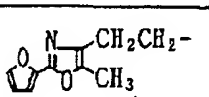
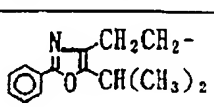
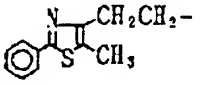
Elemental Analysis for $C_{25}H_{26}N_2O_5$:			
Calcd. :	C, 69.11;	H, 6.03;	N, 6.45
Found :	C, 69.18;	H, 6.01;	N, 6.46

Example 17 to Example 22

In substantially the same manner as in Example 16, compounds set forth in [Table 4] were obtained.

[Table 4]



Example No.	R 22	Yield (%)	m.p. (℃)	Recrystallization solvent
17		87	143-144	dichloromethane-methanol
18		77	162-163	ethyl acetate - hexane
19		57	169-170	dichloromethane-methanol
20		59	153-154	dichloromethane-methanol
21		34	154-155	ethyl acetate - hexane - isopropyl ether
22		89	127-128	ethyl acetate - hexane

Example 23

In substantially the same manner as in Example 16, 5-[3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]-2-propenylidene]-2,4-oxazolidinedione was subjected to catalytic hydrogenation to give 5-[3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]propyl]-2,4-oxazolidinedione. The product was recrystallized from chloroform-methanol-isopropyl ether to give colorless crystals, m.p.169-171°C.

Elemental Analysis for $C_{23}H_{23}N_3O_5 \cdot 1/2H_2O$:

Calcd.: C, 64.18; H, 5.62; N, 9.76

Found : C, 64.31; H, 5.70; N, 9.48

Example 24

A mixture of ethyl 2-hydroxy-4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butyrate (0.45 g),

powdery potassium cyanate (0.24 g) and butanol (20 ml) was heated for 4 days under reflux. The solvent was distilled off under reduced pressure, and the residue was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and concentrated. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with chloroform-methanol (100:3) was obtained 5-[2-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]ethyl]-2,4-oxazolidinedione (0.28 g, 63%). The product was recrystallized from dichloromethane-ethanol to give colorless prisms, m.p.193-194°C.

Elemental Analysis for $C_{23}H_{22}N_2O_5$:			
Calcd. :	C, 67.97;	H, 5.46;	N, 6.89
Found :	C, 67.92;	H, 5.61;	N, 6.64

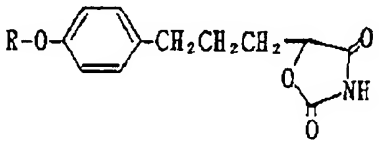
Example 25

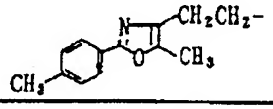
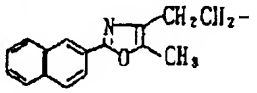
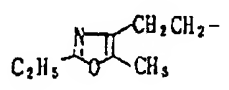
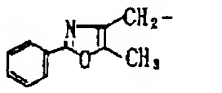
A mixture of 5-[4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butylidene]-2,4-oxazolidinedione (0.38 g), palladium-carbon (10%, 0.2 g) and tetrahydrofuran (40 ml) was subjected to catalytic hydrogenation at room temperature and 3 atom. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with chloroform-methanol (100:3) was obtained 5-[4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butyl]-2,4-oxazolidinedione (0.25 g, 65%). This product was recrystallized from dichloromethane-methanol to give colorless prisms, m.p.136-137°C.

Example 26 to Example 29

In substantially the same manner as in Example 16, compounds shown in Table 5 were obtained.

[Table 5]



Example No.	R	Yield (%)	m.p. (°C)	Recrystallization solvent
26		65	168-169	dichloromethane-methanol
27		79	163-164	dichloromethane-methanol
28		73	138-139	dichloromethane-isopropyl ether
29		52	157-158	ethyl acetate - hexane

Example 30

In substantially the same manner as in Example 16, was obtained 5-[3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-yl]propyl]-2,4-oxazolidinedione. The yield was 80%. Recrystallization of this product from dichloromethanemethanol gave colorless needles, m.p.184-185°C

Example 31

In substantially the same manner as in Example 16, 5-[5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4-pentadienylidene]-2,4-oxazolidinedione was subjected to catalytic hydrogenation to give 5-[5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]pentyl]-2,4-oxazolidinedione. The yield was 77%. Recrystallization from dichloromethane-methanol gave colorless needles, m.p.157-158°C

Example 32

In substantially the same manner as in Example 24, 5-[2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]ethyl]-2,4-oxazolidinedione was obtained. The yield was 35%. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.158- 159°C.

Example 33

To a solution of 5-[5-(4-hydroxyphenyl)pentyl]-2,4-oxazolidinedione (0.9 g) in N,N-dimethylformamide (DMF) (40 ml) was added sodium hydride (60% in oil, 0.28 g). The mixture was stirred for 15 minutes at room temperature, to which was then added 4-chloromethyl-5-methyl-2-phenyloxazole (0.85 g), and the mixture was stirred for 2 hours at 70°C. The reaction mixture was poured into water, acidified with 2N HCl, and subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and then the solvent was distilled off. The oily residue was subjected to a silica gel column chromatography. From the fractions eluted with ethyl acetate - chloroform (1:5, v/v) was obtained 5-[5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]pentyl]-2,4-oxazolidinedione (0.86 g, 58%). Recrystallization from dichloromethane - isopropyl ether gave colorless prisms, m.p.120-121°C.

Example 34

In substantially the same manner as in Example 33, was obtained 5-[4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]butyl]-2,4-oxazolidinedione. The yield was 32%. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms, m.p.186-187°C.

Example 35

A mixture of 4-[4-[2-(1,3-dioxolan-2-yl)ethyl]phenoxyacetyl]-5-methyl-2-phenyloxazole (1.8 g), 2,4-oxazolidinedione (0.925 g), piperidine (0.12 g) and acetic acid (30 ml) was heated for 15 hours under reflux. The reaction mixture was concentrated under reduced pressure. To the concentrate was added a saturated aqueous solution of sodium hydrogencarbonate, followed by extraction with chloroform. The chloroform layer was washed with water, dried ($MgSO_4$), followed by distilling off the solvent. The oily residue was subjected to a silica gel column chromatography. From the fractions eluted with methanol-chloroform (1:30, v/v) was obtained 5-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]phenyl]propylidene]-2,4-oxazolidinedione. This compound was dissolved in tetrahydrofuran (THF) (30 ml), to which was added palladium-carbon (5%, 0.3 g). The mixture was subjected to catalytic hydrogenation. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The oily residue was subjected to a silica gel column chromatography. From the fractions eluted with ethyl acetate - hexane (1:1, v/v), 5-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.32 g, 16%) was obtained as an oily product.
NMR (δ ppm in $CDCl_3$): 1.7-2.1(4H,m), 2.63(2H,t,J=7Hz), 2.74(3H,s), 4.84(1H,dd,J=7&4.5Hz), 5.37(2H,s), 6.92(2H,d,J=9Hz), 7.09(2H,d,J=9Hz), 7.45-7.55(3H,m), 7.95-8.1(3H,m).

Example 36

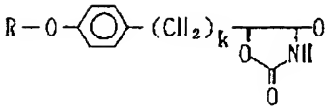
To a solution of 5-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.2 g) in tetrahydrofuran (THF) (5 ml) - ethanol (5 ml) was added sodium borohydride (0.03 g). The mix-

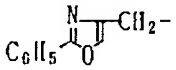
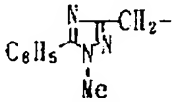
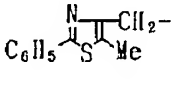
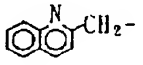
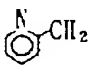
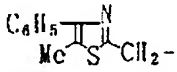
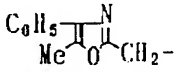
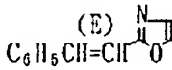
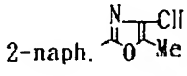
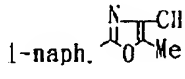
ture was stirred for one hour at room temperature. To the reaction mixture were added 2N HCl and water, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The oily residue was subjected to a silica gel column chromatography. From the reactions eluted with chloroform-methanol (50:1, v/v) was obtained 5-[3-[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propyl]-2,4-oxazolidinedione (0.16 g, 80%). Recrystallization from dichloromethane - isopropyl ether gave colorless needles, m.p.146-147°C.

Example 37 - Example 50

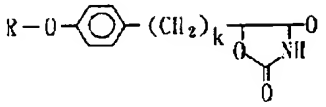
In substantially the same manner in Example 33, compounds shown in Table 6 were obtained.

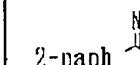
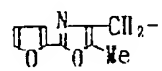
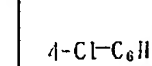
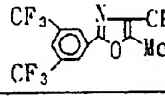
[Table 6]



Example No.	R	k	Yield (%)	m.p. (℃)	Recrystallization solvent
37		3	72	167-168	dichloromethane-methanol
38		3	66	148-149	dichloromethane isopropyl ether
39		3	71	104-105	dichloromethane isopropyl ether
40		3	23	177-178	dichloromethane-methanol
41		3	77	196-197	dichloromethane-methanol
42		3	75	137-138	dichloromethane-methanol
43		3	81	121-122	dichloromethane-methanol
44		3	80	155-156	dichloromethane-methanol
45		3	84	151-152	dichloromethane-methanol
46		3	72	oily 1) product	———

[Table 6] (continued)



Example No.	R	k	Yield (%)	m.p. (℃)	Recrystallization solvent
47		5	79	159-160	dichloromethane-methanol
48		3	74	146-147	dichloromethane isopropyl ether
49		3	70	148-149	dichloromethane-methanol
50		3	64	184-185	dichloromethane isopropyl ether

Note 1) NMR(δ ppm in $CDCl_3$): 1.7-2.1(4H, m), 2.50(3H, s), 2.62(2H, t, J=7Hz), 4.79(1H, dd, J=6.5&4.5Hz), 5.07(2H, s), 6.99(2H, d, J=8.5Hz), 7.10 (2H, d, J=8.5Hz), 7.45-7.7(3H, m), 7.85-8.0(2H, m), 8.15(1H, dd, J= 7&1Hz), 9.21(1H, d, J=8.5Hz).

Me : methyl, 2-naph. : 2-naphthyl, 1-naph. : 1-naphthyl

Example 51

A mixture of 4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]cinnamaldehyde (4.00 g), 2,4-oxazolidinedione (2.86g), piperidine (0.60 g) and ethanol (50 ml) was heated for 2 hours under reflux. The reaction mixture was concentrated and the residue was subjected to silica gel column chromatography. Fractions eluted with ethyl acetate-chloroform (1:4) gave crystals. The crystals were dissolved in tetrahydrofuran (100 ml). To the solution was added palldium-carbon (5%, 1.40 g). The mixture was subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. From the fractions eluted with chloroform-methanol (100:2), 5-[3-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]phenyl]propyl]-2,4-oxazolidinedione (1.10 g, 21%) was obtained. Recrystallization from dichloromethane-isopropylether gave colorless prisms. Melting point: 126-127°C.

Example 52

In substantially the same manner as in Example 51, 5-[3-[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]propyl]-2,4-oxazolidinedione was obtained as an oily substance. Yield: 22%.

NMR (δ ppm in $CDCl_3$): 1.7-2.15(4H,m), 2.48(3H,s), 2.61(2H,t,J=7Hz), 4.84(1H,dd,J=6.5&4.5Hz), 5.27(2H,s), 6.76(1H,d,J=8.5Hz), 7.3-7.5(4H,m), 7.95-8.1(3H,m), 8.84(1H,br s).

Example 53

In substantially the same manner as in Example 35, 5-[4-[4-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]butyl]-2,4-oxazolidinedione was obtained. Yield: 22%. Recrystallization from dichloromethane-

methanol gave colorless prisms.
Melting point: 163-164°C.

Example 54

In substantially the same manner as in Example 35, 5-[3-[2-(2-naphthylmethyl)benzoxazol-5-yl]propyl]-2,4-oxazolidinedione was obtained. Yield: 13%. Recrystallization from dichloromethane-methanol gave colorless prisms. Melting point: 151-152°C.

Example 55

In substantially the same manner as in Example 1, 5-[3-[3-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propenylidene]-2,4-oxazolidinedione was obtained. Recrystallization from chloroform-methanol gave colorless needles. Melting point: 229-230°C.

Example 56

In substantially the same manner as in Example 16, 5-[3-[3-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione was obtained. Recrystallization from ethyl acetate-hexane gave colorless needles. Melting point: 134-135°C.

Example 57

In substantially the same manner as in Example 51, 5-[3-(4-isopropoxyphenyl)propyl]-2,4-oxazolidinedione was obtained as an oily substance.
NMR (δ ppm in $CDCl_3$): 1.32(6H,d,J=6Hz), 1.65-2.15(4H,m), 2.62(2H,t,J=7Hz), 4.4-4.6(1H,m), 4.84(1H,dd,J=7&4.5Hz), 6.81(2H,d,J=8.5Hz), 7.06(2H,d,J=8.5Hz), 8.00(1H,broad s).

Example 58

In substantially the same manner as in Example 51, 5-[5-(4-isopropoxyphenyl)pentyl]-2,4-oxazolidinedione was obtained as an oily substance.
NMR (δ ppm in $CDCl_3$): 1.32(6H,d,J=6Hz), 1.3-2.1(8H,m), 2.54(2H,t,J=7.5Hz), 4.4-4.6(1H,m), 4.84(1H,dd,J=7.5&4.5Hz), 6.80(2H,d,J=8.5Hz), 7.05(2H,d,J=8.5Hz), 7.98(1H,broad s).

Example 59

In substantially the same manner as in Example 35, 5-[4-(4-isopropoxyphenyl)butyl]-2,4-oxazolidinedione was obtained by reacting 2-[3-(4-isopropoxyphenyl)propyl]-1,3-dioxolane with 2,4-oxazolidinedione, followed by allowing the reaction product to catalytic hydrogenation. Recrystallization from dichloromethane-isopropylether gave colorless prisms. Melting point: 81-82°C.

Example 60

In substantially the same manner as in Example 51, 5-[3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]butyl]-2,4-oxazolidinedione was obtained as pale yellow amorphous powder.
NMR(δ ppm in $CDCl_3$): 1.25(3H,d,J=6.8Hz), 1.30-2.00(4H,m), 2.43(3H,s), 2.55-2.80(1H,m), 4.67-4.83(1H,m), 4.97(2H,s), 6.95(2H,d,J=8.8Hz), 7.09(2H,d,J=8.8Hz), 7.35-7.53(3H,m), 7.92-8.10(2H,m).

Example 61

In substantially the same manner as in Example 33, 5-[3-[4-[2-(2-benzo[b]thienyl)-5-methyl-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione was obtained. The yield was 76%. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms, m.p. 154-155°C.

Example 62

In substantially the same manner as in Example 33, 5-[3-[4-[2-(2-benzo[b]furanyl)-5-methyl-4-oxazolyl-

methoxy]phenyl]propyl]-2,4-oxazolidinedione was obtained. The yield was 70%. Recrystallization from dichloromethane-isopropyl ether gave colorless needles, m.p. 165-166°C.

Formulation Example 1 (Preparation of tablets)

(1) 5-[3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]propyl]-2,4-oxazolidinedione	10 g
(2) lactose	50 g
(3) corn starch	15 g
(4) carboxymethylcellulose calcium	44 g
(5) magnesium stearate	1 g
	1000 tablets 120 g

The whole amounts of above (1), (2) and (3), and 30 g of (4) were kneaded with water, which was subjected to vacuum drying, followed by granulation. Thus-granulated powder was mixed with 14 g of (4) and 1 g of (5), followed by tableting using a tableting machine to prepare 1000 tablets containing 10 mg of (1) per tablet.

Formulation Example 2 (Preparation of tablets)

(1) 5-[2-[4-[2-(5-methyl-2-phenyl-4-oxazolyl]-ethoxy]phenyl]ethyl]-2,4-oxazolidinedione	30 g
(2) lactose	50 g
(3) corn starch	15 g
(4) carboxymethylcellulose calcium	44 g
(5) magnesium stearate	1 g
1000 tablets	140 g

The whole amounts of above (1), (2) and (3), and 30 g of (4) were kneaded with water, which was subjected to vacuum drying, followed by granulation. Thus-granulated powder was mixed with 14 g of (4) and 1 g of (5), which was tableted by using a tableting machine to prepare 1000 tablets containing 30 mg of (1) per tablet.

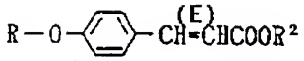
Reference Example 1

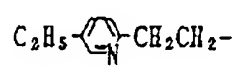
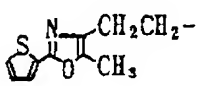
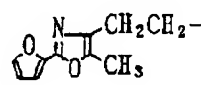
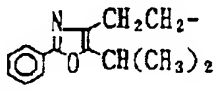
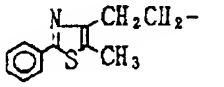
To a solution of triethyl phosphonoacetate (1.79 g) in N,N-dimethylformamide (40 ml) was added, little by little at 0°C, sodium hydride (60% in oil, 0.32 g). The mixture was stirred for 15 minutes at the same temperature. To the reaction mixture was added 4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]benzaldehyde (2.44 g), and the mixture was stirred for one hour at room temperature. The reaction mixture was poured into ice-water, which was acidified with 2N HCl, and resulting crystalline precipitate was collected by filtration. Recrystallization from ethyl acetate - hexane gave ethyl (E)-4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]cinnamate (2.52 g, 85%) as colorless needles, m.p.90-91°C.

Reference Example 2 to Reference Example 6

In substantially the same manner as in Reference Example 1, compounds shown in [Table 7] were obtained.

[Table 7]



Reference Example No.	R	R^2	Yield (%)	m.p. (℃)	Recrystallization solvent
2		CH_3	83	84- 85	ethyl ether - hexane
3		C_2H_5	90	77- 78	ethyl ether - hexane
4		C_2H_5	88	81- 82	ethyl ether - hexane
5		C_2H_5	95	69- 70	hexane
6		C_2H_5	96	121-122	ethyl acetate - hexane

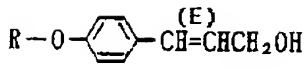
Reference Example 7

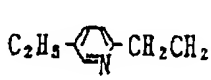
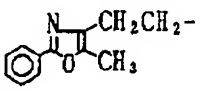
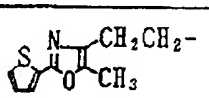
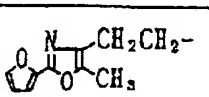
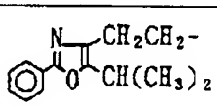
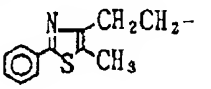
A toluene solution of diisobutylaluminum hydride (1.5M, 9.3 ml) was added dropwise at 0°C to a suspension of ethyl (E)-4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]cinnamate (2.48 g) in dichloromethane (50 ml). The mixture was stirred for 2 hours at room temperature, to which were then added, under ice-cooling, methanol (3 ml) and, then, water (30 ml). The mixture was subjected to filtration through a celite layer. The organic layer was washed with water, dried ($MgSO_4$) and, then, concentrated. The concentrate was purified by means of a column chromatography. From the fractions eluted with ethyl acetate - hexane (1:1) was obtained (E)-3-[4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]phenyl]-2-propen-1-ol (1.44 g, 65%). Recrystallization from dichloromethane - isopropyl ether gave colorless prisms, m.p.116-117°C.

Reference Example 8 to Reference Example 13

In substantially the same manner as in Reference Example 7, compounds shown in [Table 8] were obtained.

[Table 8]



Reference Example No.	R	Yield (%)	m.p. (°C)	Recrystallization solvent
8		81	Note 1) oily product	———
9		90	127-128	ethyl acetate
10		68	124-125	dichloromethane-isopropyl ether
11		81	113-114	dichloromethane-isopropyl ether
12		29	110-111	ethyl acetate - hexane
13		85	139-140	ethyl acetate

Note 1) NMR(δ ppm in $CDCl_3$) : 1.24(3H, t, J=7.5Hz), 2.63(2H, q, J=7.5Hz), 3.23(2H, t, J=7Hz), 4.25-4.4(4H, m), 6.23(1H, dt, J=16&6Hz), 6.55 (1H, d, J=16Hz), 6.86(2H, d, J=9Hz), 7.19(1H, d, J=8Hz), 7.30(2H, d, J=9Hz), 7.46(1H, dd, J=8&2Hz), 8.40(1H, d, J=2Hz).

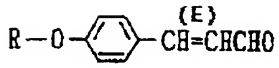
Reference Example 14

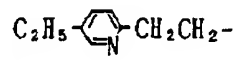
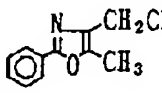
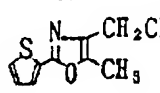
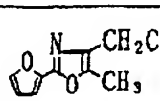
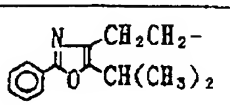
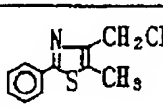
Activated manganese dioxide (2.8 g) was added to a solution of (E)-3-[4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]phenyl]-2-propen-1-ol (1.4 g) in dichloromethane (50 ml). The mixture was stirred for 2 hours at room temperature, which was subjected to filtration through celite. The filtrate was concentrated to give (E)-4-[2-[5-methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]cinnamaldehyde (1.27 g, 91%). Recrystallization from dichloromethane - isopropyl ether gave colorless needles, m.p.110-111°C.

Reference Example 15 to Reference Example 20

In substantially the same manner as in Reference Example 14, compounds shown in [Table 9] were obtained.

[Table 9]



Reference Example No.	R	Yield (%)	m.p. (°C)	Recrystallization solvent
15		84	50- 51	ethyl ether - hexane
16		94	128-129	ethyl acetate - hexane
17		97	120-121	dichlromethane-isopropyl ether
18		93	103-104	dichloromethane-isopropyl ether
19		93	133-134	ethyl acetate-ethyl ether
20		88	128-129	ethyl acetate-hexane

Reference Example 21

To a solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (3.0 g) and pyruvic acid (3.44 g) in methanol (80 ml) was added dropwise a solution of sodium carbonate (4.14 g) in water (80 ml). The mixture was stirred for 24 hours at temperatures ranging from 70 to 80°C, which was poured into water, followed by washing with ethyl acetate. The aqueous layer was acidified with conc. HCl, then resulting crystalline prepcipitate was collected by filtration. The crystals were added to ethanol containing hydrogen chloride (5%, 15 ml), and the mixture was heated for 30 minutes under reflux. The solvent was distilled off under reduced pressure. The residue was dissolved in chloroform. The solution was washed with water, dried ($MgSO_4$) and, then, concentrated. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with ethyl acetate - chloroform (1:9) was obtained ethyl (E)-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene pyruvate (1.0 g, 25%). Recrystallization from dichloromethane-ethanol gave pale yellow needles, m.p.99-100°C

Reference Example 22

A mixture of ethyl (E)-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene pyruvate (0.85 g), palladium-carbon (10%, 0.1 g) and dioxane (80 ml) was subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The catalyst was filtered off. The filtrate was concentrated under reduced pressure. The concentrate was dissolved in ethanol (20 ml). To the solution was added, under ice-cooling, sodium borohydride (0.08 g), and the mixture was stirred for one hour at room temperature. The reaction mixture was poured into water and neutralized with 1N HCl, followed by extraction with ethyl acetate. The ethyl acetate

layer was washed with water, dried ($MgSO_4$) and, then concentrated. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with chloroform - ethyl acetate (9:1) was obtained ethyl 2-hydroxy-4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butyrate (0.55 g, 64%). Recrystallization from ethyl ether - hexane gave colorless needles, m.p.67-68°C.

Reference Example 23

To a stirred solution of 2-chloro-5-nitropyridine (25 g), 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol (32.1 g) in THF (250 ml) was added portionwise, under ice-cooling, sodium hydride (60% in oil, 6.92 g). The reaction mixture was stirred for further 15 hours at room temperature, which was poured into water, followed by extraction with ethyl acetate. The ethyl acetate was washed with water and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure. The residual crystals were collected by filtration. Recrystallization from ethanol gave 2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-nitropyridine (25.4 g, 49%) as yellowish brown crystals, m.p.110.5-111.5°C.

Elemental Analysis for $C_{17}H_{15}N_3O_4$:			
Calcd. :	C, 62.76;	H, 4.65;	N, 12.92
Found :	C, 62.80;	H, 4.58;	N, 12.96

Reference Example 24

A mixture of 2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-nitropyridine (13.4 g), palladiumcarbon (5%, 1.5 g) and ethyl acetate (200 ml) - methanol (150 ml) was subjected catalytic hydrogenation at room temperature under one atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residual crystals were collected by filtration to obtain 5-amino-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (11.4 g, 93%). Recrystallization from ethyl acetate - hexane gave brown crystals, m.p.107.0-108.0°C.

Elemental Analysis for $C_{17}H_{17}N_3O_2$:			
Calcd. :	C, 69.14;	H, 5.80;	N, 14.23
Found :	C, 69.01;	H, 5.94;	N, 13.99

Reference Example 25

To a mixture of 5-amino-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (10.0 g), conc. HCl (8.47 ml) and acetone (100 ml) was added dropwise a solution of sodium nitrite ($NaNO_2$) (2.46 g) in water (10 ml) at temperatures below 10°C. The mixture was stirred for 30 minutes at 10°C, to which was dropwise added a solution of potassium iodide (KI) (2.46 g) in water (10 ml) at 10°C. The reaction mixture was stirred for further one hour at temperatures raging from 30 to 35°C and for another one hour at temperatures ranging from 35 to 40°C, followed by concentration under reduced pressure. The concentrate was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure. The residual oily product was subjected to a silica gel chromatography. From the fractions eluted with ethyl acetate - hexane (1:3, v/v) was obtained 5-iodo-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (7.22 g, 52%). Recrystallization from ethyl acetate - hexane gave colorless crystals, m.p.105-106°C.

Elemental Analysis for $C_{17}H_{15}N_2O_2I$:			
Calcd. :	C, 50.26;	H, 3.72;	N, 6.90
Found :	C, 50.22;	H, 3.89;	N, 6.78

Reference Example 26

To a solution of 5-iodo-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (2.5 g) in tetrahydrofuran (40 ml) was added dropwise, at -65°C under nitrogen streams, a hexane solution of n-butyllithium (1.6M, 4.61 ml). The mixture was stirred for 15 minutes at the same temperature, to which was added dropwise N,N-dimethylformamide (0.71 ml). The cooling bath was removed, then the reaction mixture was stirred for further 30 minutes, to which was added a saturated aqueous solution of ammonium chloride (6 ml). The reaction mixture was poured into water, followed by extraction with ethyl acetate. The ethyl acetate was washed with water and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure to leave 5-formyl-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (1.5 g, 79%). Recrystallization from ethyl acetate - hexane gave colorless crystals, m.p.99-100°C.

Elemental Analysis for $C_{18}H_{16}N_2O_3$:			
Calcd. :	C, 70.12;	H, 5.23;	N, 9.09
Found :	C, 69.94;	H, 5.38;	N, 8.94

Reference Example 27

In substantially the same manner as in Reference Example 1, was obtained methyl 3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl]ethoxy]-5-pyridyl]acrylate. Recrystallization from ethyl acetate gave colorless crystals, m.p.138-139°C.

Reference Example 28

In substantially the same manner as in Reference Example 7, (E)-3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl-ethoxy]-5-pyridyl]-2-propen-1-ol was obtained. Recrystallization from ethyl acetate - isopropyl ether gave colorless crystals, m.p.115-116°C.

Reference Example 29

In substantially the same manner as in Reference Example 14, (E)-3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]acrolein. Recrystallization from ethyl acetate - hexane gave colorless crystals, m.p.138-139°C.

Reference Example 30

A mixture of methyl 2-bromo-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionate (15.0 g), 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) (6.2 g) and toluene (200 ml) was stirred for 2 hours at 70°C. The reaction mixture was poured into ethyl acetate (200 ml), which was washed with 2N HCl and a saturated aqueous saline solution, followed by drying ($MgSO_4$). The solvent was distilled off under reduced pressure to leave methyl 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamate (10.8 g, 88%). Recrystallization from ethyl acetate - hexane colorless needles, m.p.114-115°C.

Reference Example 31

Sodium hydride (60% in oil, 0.78 g) was added in limited amounts, at room temperature, to a solution of [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide (8.9 g) in N,N-dimethylformamide (100 ml). The mixture was stirred for 30 minutes at the same temperature range, to which was added 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (5.0 g). The mixture was stirred for 15 minutes at room temperature, then for 5 hours at 70°C. The reaction mixture was poured into ice-water, which was acidified with 2N HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The residue was purified by means of a silica gel column chromatography. From the fractions eluted with hexane - ethyl acetate (3:1), (Z)-2-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2-propenyl]-1,3-dioxane (5.1 g, 77%) was obtained as an oily product.
NMR (δ ppm in $CDCl_3$): 1.25-1.4(1H,m), 1.95-2.25(1H,m), 2.37(3H,s), 2.66(1H,ddd,J=7&5&2Hz),

2.98(2H,t,J=6.5Hz), 3.7-3.85(2H,m), 4.0-4.3(4H,m), 4.63(1H,t,J=5Hz), 5.64(1H,dt,J=11.5&7Hz), 6.48(1H,br d,J=11.5Hz), 6.85(2H,d,J=9Hz), 7.22(2H,d,J=9Hz), 7.35-7.5(3H,m), 7.9-8.0(2H,m).

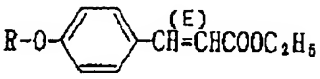
Reference Example 32

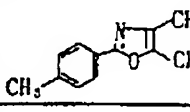
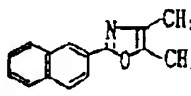
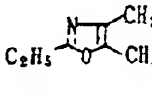
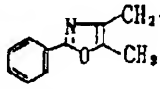
A mixture of (Z)-2-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2-propenyl]-1,3-dioxane (5.0 g), palladium-carbon (5%, 0.1 g) and ethanol (100 ml) was subjected to catalytic hydrogenation at room temperature under one atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The concentrate was purified by means of a silica gel column chromatography. From the fractions eluted with hexane - ethyl acetate (1:1), 2-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propyl]-1,3-dioxane (4.8 g, 96%) was obtained.
NMR (δ ppm in $CDCl_3$): 1.25-1.4(1H,m), 1.5-1.8(4H,m), 1.9-2.2(1H,m), 2.37(3H,s), 2.54(2H,t,J=7Hz), 2.96(2H,t,J=6.5Hz), 3.65-3.85(2H,m), 4.0-4.15(2H,m), 4.21(2H,t,J=6.5Hz), 4.50(1H,t,J=5Hz), 6.80(2H,d,J=9Hz), 7.06(2H,d,J=9Hz), 7.35-7.5(3H,m), 7.9-8.0(2H,m).

Reference Example 33 to Reference Example 36

In substantially the same manner as in Reference Example 1, compounds shown in [Table 10] were obtained.

[Table 10]



Reference Example No.	R	Yield (%)	m.p. (℃)	Recrystallization solvent
33		88	126-127	diethyl ether - isopropyl ether
34		86	111-112	dichloromethane-isopropyl ether
35		89	oily product[1]	
36		96	145-146	ethyl acetate-hexane

Note 1) NMR(δ ppm in $CDCl_3$) : 1.30(3H, t, J=7.5Hz), 1.33(3H, t, J=7Hz), 2.25(3H, s), 2.70(2H, q, J=7.5Hz), 2.88(1H, t, J=7Hz), 4.20 (2H, t, J=7Hz), 4.25(2H, q, J=7.5Hz), 6.29(1H, d, J=16Hz), 6.88 (2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.63(1H, d, J=16Hz).

Reference Example 37

In substantially the same manner as in Reference Example 1, by reaction of 5-formyl-2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran with triethyl phosphonoacetate, was obtained ethyl (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-yl]acrylate. Yield was 74%. Recrystallization from ether-hexane gave colorless prisms, m.p. 150-151°C.

Reference Example 38

In substantially the same manner as in Reference Example 1, by reaction of (E)-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamaldehyde with triethyl phosphonoacetate, was obtained ethyl (E)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4-pentadienoate. The yield was 56%. Recrystallization from ether-hexane gave colorless needles, m.p. 102-103°C.

Reference Example 39

A mixture of 4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzaldehyde (2.9 g), sodium pyruvate (3.3 g), sodium carbonate (3.2 g), water (80 ml) and methanol (80 ml) was stirred for 6 hours under reflux. The reaction mixture was concentrated under reflux to about 1/3 of the initial volume. The concentrate was subjected to extraction with ethyl acetate. The aqueous layer was acidified with conc: HCl. Resulting crystalline precipitate was collected by filtration to obtain (E)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzylidenepyruvic acid (1.6 g, 44%). Recrystallization from chloroform-methanol gave colorless needles, m.p.197-198°C.

Reference Example 40

To a mixture of (E)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzylidenepyruvic acid (1.3 g) and ethanol (50 ml) was added conc. sulfuric acid (0.1 ml). The mixture was heated for 8 hours under reflux, then the reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), followed by distilling off the solvent. The residue was subjected to a silica gel column chromatography. From the fractions eluted with ethyl acetate - hexane (1:3, v/v), ethyl (E)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzylidenepyruvate (1,2 g, 86%) was obtained. Recrystallization from ethyl acetate - hexane gave pale yellow prisms. Melting point: 110-111°C

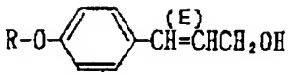
Reference Example 41

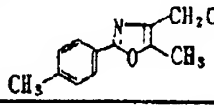
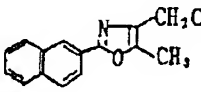
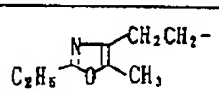
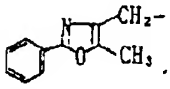
In substantially the same manner as in Reference Example 22, from ethyl (E)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzylidenepyruvate, was obtained ethyl 2-hydroxy-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy]phenyl]butyrate. The yield was 89%. NMR (δ ppm $CDCl_3$): 1.28(3H,t,J=7Hz), 1.8-2.2(2H,m), 2.43(3H,s), 2.71(2H,t,J=7Hz), 2.84(1H,d,J=5.2Hz), 4.1-4.3(1H,m), 4.21(2H,q,J=7Hz), 4.97(2H,s), 6.94(2H,d,J=9Hz), 7.13(2H,d,J=9Hz), 7.4-7.5(3H,m), 7.95-8.1(2H,m).

Reference Example 42 to Reference Example 45

In substantially the same manner as in Reference Example 7, compounds shown in [Table 11] were obtained.

[Table 11]



Reference Example No.	R	Yield (%)	m.p. (℃)	Recrystallization solvent
42		84	123-124	dichloromethane-isopropyl ether
43		81	134-135	dichloromethane-isopropyl ether
44		34	oily product[1)]	
45		97	133-134	ethyl acetate - hexane

Note 1) NMR(δ ppm in $CDCl_3$) : 1.30(3H, t, J=7.5Hz), 1.3-1.5(1H, m), 2.45(3H, s), 2.70(2H, q, J=7.5Hz), 2.87(2H, t, J=7Hz), 4.17 (2H, t, J=7Hz), 4.25-4.35(2H, m), 6.23(1H, dt, J=16&6Hz), 6.55 (1H, d, J=16Hz), 6.83(2H, d, J=9Hz), 7.30(2H, d, J=9Hz).

Reference Example 46

In substantially the same manner as in Reference Example 7, ethyl (E)-3-[2-(5-methyl-2-phenyl-4-oxazolyl methyl)benzofuran-5-yl]acrylate was subjected to reduction to give (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-yl]-2-propen-1-ol. The yield was 57%. Recrystallization from dichloromethanehexane gave colorless needles, m.p. 156-157°C.

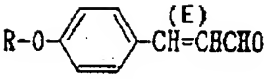
Reference Example 47

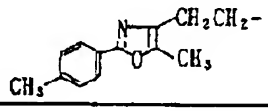
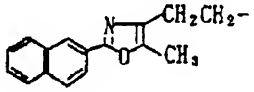
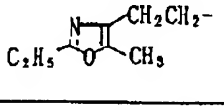
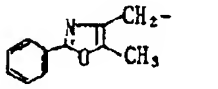
In substantially the same manner as in Reference Example 7, ethyl (E,E)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4-pentadienoate was subjected to reduction to give (E,E)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4-pentadien-1-ol. The yield was 63%. Recrystallization from dichloromethane-hexane gave colorless scales, m.p.132-133°C.

Reference Example 48 to Reference Example 51

In substantially the same manner as in Reference Example 14, compounds shown in [Table 12] were obtained.

[Table 12]



Reference Example No.	R	Yield (%)	m.p. (℃)	Recrystallization solvent
48		84	115-116	dichloromethane-isopropyl ether
49		91	155-156	dichloromethane-isopropyl ether
50		95	oily product[1)]	
51		70	114-115	ethyl acetate-hexane

Note 1) NMR(δ ppm in $CDCl_3$) : 1.30(3H, t, J=7.5Hz), 2.25(3H, s), 2.71 (2H, q, J=7.5Hz), 2.90(2H, t, J=6.5Hz), 4.23(2H, t, J=6.5Hz), 6.60 (1H, dd, J=16&7.5Hz), 6.93(2H, d, J=9Hz), 7.41(1H, d, J=16Hz), 7.50 (2H, d, J=9Hz), 9.65(1H, d, J=7.5Hz).

Reference Example 52

In substantially the same manner as in Reference Example 14, from (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-yl]-2-propen-1-ol, was obtained (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-yl]acrolein. The yield was 93%. Recrystallization from dichloromethane-hexane gave colorless needles, m.p.136-137°C.

Reference Example 53

In substantially the same manner as in Reference Example 14, from (E,E)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4-pentadien-1-ol, was obtained (E,E)-5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-2,4- pentadien-1-al. The yield was 82%. Recrystallization from dichloromethane-hexane gave yellow prisms, m.p.133-134°C.

Reference Example 54

A mixture of 4-bromoacetyl-5-methyl-2-phenyloxazole (2.60 g), 4-[2-(1,3-dioxolan-2-yl)ethyl]phenol (1.82 g), potassium carbonate (1.28 g) and 2-butanone (60 ml) was stirred for 20 hours at temperatures ranging from 70 to 80°C. The reaction mixture was poured into water. Resulting crystalline precipitate was collected by filtration, which was purified by means of a silica gel column chromatography. From the fractions eluted with chloroform-methanol (100:1, v/v), 4-[4-[2-(1,3-dioxolan-2-yl)ethyl]phenoxyacetyl]-5-methyl-2-phenyloxazole (2.08g, 57%) was obtained. Recrystallization from dichloromethane - isopropyl ether gave colorless prisms, m.p.119-120°C.

Reference Example 55

In substantially the same manner as in Reference Example 1, ethyl 4-[2-[N-methyl-N-(2-pyridyl)amino]-

ethoxy]cinnamate was obtained. Yield: 97%. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms. Melting point 80-81°C.

Reference Example 56

In substantially the same manner as in Reference Example 1, ethyl (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]acrylate was obtained. Yield: 86%. Recrystallization from dichloromethaneisopropyl ether gave colorless prisms. Melting point: 109-110°C.

Reference Example 57

In substantially the same manner as in Reference Example 7, (E)-3-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]phenyl]-2-propen-1-ol was obtained as an oily substance. Yield: 87%.
NMR (δ ppm in $CDCl_3$): 3.14(3H,s), 3.98(2H,t,J=5.5Hz), 4.19(2H,t,J=5.5Hz), 4.29(2H,br d, J=5.5Hz), 6.22(1H,dt,J=16&6Hz), 6.45-6.6(3H,m), 6.85(2H,d,J=9Hz), 7.30(2H,d,J=9Hz), 7.45(1H,ddd,J=8.5&7&2Hz), 8.1-8.2(1H,m).

Reference Example 58

In substantially the same manner as in Reference Example 7, (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]-2-propen-1-ol was obtained. Yield: 57%. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms. Melting point: 116-117°C.

Reference Example 59

In substantially the same manner as in Reference Example 14, 4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]cinnamaldehyde was obtained as an oily substance. Yield: 100%.
NMR (δ ppm in $CDCl_3$): 3.15(3H,s), 4.01(2H,t,J=5.5Hz), 4.25(2H,t,J=5.5Hz), 6.5-6.7(3H,m), 6.95(2H,d,J=9Hz), 7.41(1H,d,J=16Hz), 7.4-7.55(3H,m), 8.16(1H,ddd,J=5&2&1Hz), 9.65(1H,d,J=8Hz).

Reference Example 60

In substantially the same manner as in Reference Example 14, (E)-3-[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]acrolein was obtained. Yield: 92%. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms. Melting point: 147-148°C.

Reference Example 61

A solution of n-butyllithium in hexane (1.62M, 25.9 ml) was added dropwise to a suspension of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide (18.6 g) in tetrahydrofuran (180 ml) at -20°C. The mixture was stirred for 2 hours. To the reaction mixture was added 4-[2-(2-naphthyl)-5-methyl-4-oxazolylmethoxy]benzaldehyde (12.0 g). The mixture was stirred at 50-55°C for 4 hours. The reaction mixture was poured into ice-water, followed by subjecting extraction with ethyl acetate.

The ethyl acetate layer was washed with 0.1N-hydrochloric acid and water in the order mentioned and dried over magnesium sulfate. The solvent was distilled off. The residue was subjected to silica gel column chromatography. From the fraction eluted with chloroform-methanol (100:5), crystals (14.8 g) were obtained. The crystals were dissolved in tetrahydrofuran (250 ml). To the solution was added palladium-carbon (5%, 3.0 g). The mixture was subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The catalyst was filtered off. The filtrate was concentrated under reflux, whereby 4-[4-[3-(1,3-dioxolan-2-yl)propyl]phenoxymethyl]-5-methyl-2-(2-naphthyl)oxazole (12.1 g, 81%) was obtained. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms. Melting point: 141-142°C.

Reference Example 62

In substantially the same manner as in Reference Example 1, ethyl (E)-4-hydroxy-3-nitrocinnamate was obtained by reacting 4-hydroxy-3-nitrobenzaldehyde with triethyl phosphonoacetate. Recrystallization from dichloromethane-isopropyl ether gave pale yellow needles. Melting point: 114-115°C.

Reference Example 63

In substantially the same manner as in Reference Example 24, ethyl 3-(3-amino-4-hydroxyphenyl)propionate was obtained as an oily substance by subjecting ethyl (E)-4-hydroxy-3-nitrocinnamate to catalytic reduction. NMR (δ ppm in $CDCl_3$): 1.24(3H,t,J=7Hz), 2.5-2.9(4H,m), 4.12(2H,q,J=7Hz), 6.49(1H,dd,J=8&2Hz), 6.60(1H,d,J=2Hz), 6.64(1H,d,J=8Hz).

Reference Example 64

A mixture of phosphorus pentoxide (P_2O_5) (12.9 g), hexamethyldisiloxane (29.5 g) and 1,2-dichlorobenzene was heated for 10 minutes under reflux. To the mixture were added ethyl 3-(3-amino-4-hydroxyphenyl)propionate (4.75 g) and 2-naphthylacetic acid (4.23 g). The mixture was heated for 3 hours under reflux. The reaction mixture was poured into water and allowed to extraction with ethyl acetate. The ethyl acetatae layer was washed with water and dried over magnesium sulfate. The solvent was distilled off, and the residue was subjected to silica gel column chromatography. From the fractions eluted with ethyl acetate-hexane (1:4, v/v), ethyl 3-[2-(2-naphthylmethyl)benzoxazol-5-yl]propionate (5.95 g, 73%) was obtained. Recrystallization from ether-isopropyl ether gave colorless needles. Melting point: 81-82°C.

Reference Example 65

To a solution of ethyl 3-[2-(2-naphthylmethyl)-benzoxazol-5-yl]propionate (5.8 g) in ether (100 ml)-tetrahydrofuran (100 ml) was added lithium aluminum hydride (0.73 g), and the mixture was stirred at room temperature for one hour. To the reaction mixture was added water (4 ml). Insolubles were filtered off. The filtrate was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (1:1, v/v), 3-[2-(2-naphthylmethyl)benzoxazol-5-yl]propanol (2.1 g, 41%) was obtained. Recrystallization from dichloromethane-isopropylether gave colorless prisms. Melting point: 102-103°C.

Reference Example 66

Oxalyl chloride[$(COCl)_2$] (0.88 g) was added dropwise to a solution of dimethyl sulfoxide (DMSO) (1.0 g) in dichloromethane (30 ml) at -30°C. To the mixture was added 3-[2-(2-naphthylmethyl)benzoxazol-5-yl]-propanol (2.0 g). The mixture was stirred for 30 minutes at the same temperature. To the mixture was added triethyl amine (3.19 g). The mixture was stirred for 30 minutes, warmed to 0°C and poured into 2N $HC\ell$. The organic layer was separated, washed with water and dried over magnesium sulfate ($MgSO_4$). The solvent was distilled off, and the residue was subjected to silica gel column chromatography. From the fractions eluted with ethyl acetate-hexane (1:2, v/v), 3-[2-(2-naphthylmethyl)benzoxazol-5-yl]propionaldehyde (1.54 g, 77%) was obtained. Recrystallization from etherisopropyl ether gave colorless needles. Melting point: 81-82°C.

Reference Example 67

A mixture of 3-[2-(2-naphthylmethyl)benzoxazol-5-yl]propionaldehyde (2.9 g), ethylene glycol (0.685 g), P-toluenesulfonic acid monohydrate (0.175 g) and benzene (50 ml) was stirred for 3 hours under reflux. The reaction mixture was successively washed with aqueous solution of sodium hydrogencarbonate and water, and dried over magnesium sulfate ($MgSO_4$). The solvent was distilled off, whereby 5-[2-(1,3-dioxolan-2-yl)ethyl]-2-(2-naphthylmethyl)benzoxazole (2.95 g, 89%) was obtained. Recrystallization from dichloromethaneisopropyl ether gave colorless prisms. Melting point: 85-86°C.

Reference Example 68

A mixture of 2-chloromethyl-5-methyl-2-phenyloxazole (20.8 g), 3-hydroxybenzaldehyde (12.2 g), potassium carbonate (27.6 g) and N,N-dimethylformamide (DMF) (200 ml) was heated at 90°C for 2 hours. The reaction mixture was poured into water, and subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate ($MgSO_4$). The solvent was distilled off, whereby 3-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzaldehyde (26.5 g, 90%) was obtained. Recrystallization from ethanol gave colorless prisms. Melting point: 67-68°C.

Reference Example 69

In substantially the same manner as in Reference Example 1, ethyl (E)-3-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamate was obtained.
Recrystallization from ethanol gave colorless prisms. Melting point: 91-92°C.

Reference Example 70

To a solution of ethyl (E)-3-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamate (14.0 g) in dichloromethane (200 ml) was added a solution of diisobutylaluminium hydride in toluene (1.5M, 51 ml) dropwise under ice cooling. The reaction mixture was stirred for 30 minutes at the same temperature, and to the mixture was added dropwise 2N-HCℓ (150 ml). The organic layer was separated, washed with water and dried over magnesium sulfate ($MgSO_4$). The solvent was distilled off, whereby (E)-[3-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propen-1-ol (11.5 g, 92%) was obtained. Recrystallization from ethyl acetate gave colorless prisms. Melting point: 120-121°C.

Reference Example 71

In substantially the same manner as in Reference Example 14, (E)-3-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamaldehyde was obtained. Recrystallization from ethanol acetate-hexane gave colorless rods. Melting point: 103-104°C.

Reference Example 72

In substantially the same manner as in Reference Example 23, 2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-nitropyridine was obtained. Recrystallization from dichloromethane-isopropyl ether gave pale yellow prisms. Melting point: 142-143°C.

Reference Example 73

In substantially the same manner as in Reference Example 24, 5-amino-2-(5-methyl-2-phenyl-4-oxazolylmethoxy)pyridine was obtained. Recrystallization from methanol-isopropyl ether gave colorless prisms. Melting point: 106-107°C.

Reference Example 74

In substantially the same manner as in Reference Example 25, 5-iodo-2-(5-methyl-2-phenyl-4-oxazolylmethoxy)pyridine was obtained. Recrystallization from ethyl-acetate gave colorless prisms. Melting point: 129-130°C.

Reference Example 75

In substantially the same manner as in Reference Example 26, 5-formyl-2-(5-methyl-2-phenyl-4-oxazolylmethoxy)pyridine was obtained. Recrystallization from ethyl acetate-hexane gave colorless prisms. Melting point: 116-117°C.

Reference Example 76

To a mixture of 4-benzyloxybenzaldehyde (4.5 g), (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide and N,N-dimethylformamide (DMF) (50 ml) was added sodium hydride (60% in oil, 0.935 g). The mixture was stirred for 3 hours at 60°C. The reaction mixture was poured into ice-water and neutralized with 2N-HCℓ. The mixture was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate ($MgSO_4$). The solvent was distilled off, and the residue was subjected to silica gel column chromatography. From the fractions eluted with chloroform, 2-vinyl-1,3-dioxolane derivative (5.7 g) was obtained as an oily substance. The oily substance was dissolved in ethanol (150 ml). To the solution was added palladium-carbon (5%, 2.0 g), and the mixture was subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. From the fractions eluted

with chloroform-ethyl acetate (50:1, v/v), 2-[2-(4-hydroxyphenyl)ethyl]-1,3-dioxolane was obtained as an oily substance.
NMR (δ ppm in $CDCl_3$): 1.85-2.0(2H,m), 2.6-2.75(2H,m), 3.8-4.15(4H,m), 4.82(1H,broad s), 4.88(1H,t,J=4.5Hz), 6.75(2H,d,J=8.5Hz), 7.07(2H,d,J=8.5Hz).

Reference Example 77

In substantially the same manner as in Reference Example 1, crude ethyl (E)-4-isopropoxycinnamate was obtained. The crude substance was subjected to silica gel column chromatography, and eluted with ether-hexane (1:5, v/v).
NMR (δ ppm in $CDCl_3$): 1.33(3H,t,J=7Hz), 1.35(6H,d,J=6Hz), 4.25(2H,q,J=7Hz), 4.5-4.7(1H,m), 6.30(1H,d,J=16Hz), 6.87(2H,d,J=9Hz), 7.46(2H,d,J=9Hz), 7.63(1H,d,J=16Hz).

Reference Example 78

In substantially the same manner as in Reference Example 7, crude (E)-3-(4-isopropoxyphenyl)-2-propen-1-ol was obtained. The crude substance was subjected to silica gel column chromatography, and eluted with ethyl acetate-hexane (1:4, v/v).
NMR (δ ppm in $CDCl_3$): 1.33(6H,d,J=6Hz), 1.38(1H,t,J=6Hz), 4.30(2H,dt,J=6&1.5Hz), 4.45-4.65(1H,m), 6.23(1H,dt,J=16&6Hz), 6.56(1H,d,J=16Hz), 6.84(2H,d,J=8.5Hz), 7.31(2H,d,J=8.5Hz).

Reference Example 79

In substantially the same manner as in Reference Example 14, (E)-4-isopropoxycinnamaldehyde was obtained as an oily substance.
NMR (δ ppm in $CDCl_3$): 1.37(6H,d,J=6Hz), 4.5-4.7(1H,m), 6.61(1H,dd,J=16&8Hz), 6.92(2H,d,J=9Hz), 7.42(1H,d,J=16Hz), 7.51(2H,d,J=9Hz).

Reference Example 80

To a solution of 5-[3-(4-isopropoxyphenyl)propyl]-2,4-oxazolidinedione (1.5 g) in dichloromethane (70 ml) was added dropwise titanium tetrachloride ($TiCl_4$) (4.1 g) at 0°C. The mixture was stirred for one hour at the same temperature. The reaction mixture was poured into ice-water, and subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate ($MgSO_4$). The solvent was distilled off, and the residue was subjected to silica gel column chromatography. From the fractions eluted with ethyl acetate-hexane (1:4, v/v), 5-[3-(4-hydroxyphenyl)propyl]-2,4-oxazolidinedione (0.755 g, 59%) was obtained. Recrystallization from acetonehexane gave colorless prisms. Melting point: 132-133°C.

Reference Example 81

To a mixture of 4-isopropoxybenzaldehyde (15.0 g), triethyl 4-phosphonocrotonate (27.3 g) and N,N-dimethylformamide (DMF) (100 ml) was added oily sodium hydride (60%, 4.38 g), and the mixture was stirred for 16 hours at room temperature. The reaction mixture was poured into ice-water, and neutralized with 2N-HCℓ. The mixture was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate ($MgSO_4$). The solvent was distilled off and the residue was subjected to column chromatography. From the fractions eluted with ether-hexane, ethyl (E,E)-5-(4-isopropoxyphenyl)-2,4-pentadienoate (13.7 g, 58%) was obtained. Recrystallization from ether-hexane gave colorless prisms. Melting point 64-65°C.

Reference Example 82

In substantially the same manner as in Reference Example 7, ethyl (E,E)-5-(4-isopropoxyphenyl)-2,4-pentadienate was reduced with diisobutylaluminium hydride to'give (E,E)-5-(4-isopropoxyphenyl)-2,4-pentadien-l-ol. Recrystallization from isopropyl ether gave colorless needles. Melting point 91-92°C.

Reference Example 83

In substantially the same manner as in Reference Example 14, (E,E)-5-(4-isopropoxyphenyl)-2,4-penta-

dien-1-ol was oxidized with manganese dioxide to give (E,E)-5-(4-isopropoxyphenyl)-2,4-pentadien-1-al as an oily substance.
NMR (δ ppm in $CDCl_3$): 1.36(6H,d,J=6Hz), 4.5-4.7(1H,m), 6.22(1H,dd,J=15&8Hz), 6.8-7.05(4H,m), 7.26(1H,dd,J=J=15&10Hz), 7.44(2H,d,J=9Hz), 9.59(1H,d,J=8Hz).

Reference Example 84

In substantially the same manner as in Reference Example 80, 5-[5-(4-hydroxyphenyl)pentyl]-2,4-oxazolidinedione was obtained. Recrystallization from ether-isopropyl ether gave colorless prisms. Melting point: 96-97°C.

Reference Example 85

To an ice-cooled solution of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide (51,0 g) in N,N-dimethylformamide (DMF) (200 ml) was added portionwise sodium hydride (60% in oil, 4.6 g), and the mixture was stirred for 15 minutes. To the mixture was added 4-isopropoxybenzaldehyde (18.0 g), and the mixture was stirred for 5 hours at 80-85°C. The reaction mixture was poured into ice water, and neutralized with 2N-HCℓ. The mixture was subjected to extraction with ether. The ether layer was washed with water and dried over magnesium sulfate. The solvent was distilled off and the residue was subjected to silica gel column chromatography. From the fractions eluted with ethyl acetate-hexane (1:4, v/v), 1,3-dioxolane derivative (14.5 g) was obtained as an oily substance.

The oily substance was dissolved in ethanol (250 ml). By using palladium-carbon (5%, 5.0 g) as catalyst, the solution was subjected to catalytic reduction at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. From the fractions eluted with ethyl acetate-hexane (1:5, v/v), 2-[3-(4-isopropoxyphenyl)propyl]-1,3-dioxolane (6.7 g, 24%) was obtained as an oily substance.
NMR (δ ppm in $CDCl_3$): 1.32(6H,d,J=6Hz), 1.6-1.8(4H,m), 2.5-2.65(2H,m), 3.8-4.0(4H,m), 4.4-4.6(1H,m), 4.8-4.9(1H,m), 6.8(2H,d,J=8.5Hz), 7.07(2H,d,J=8.5Hz).

Reference Example 86

In substantially the same manner as in Reference Example 80, 5-[4-(4-hydroxyphenyl)butyl]-2,4-oxazolidinedione was obtained. Recrystallization from dichloromethane-methanol gave colorless prisms.
Melting point: 151-152°C.

Reference Example 87

In substantially the same manner as in Reference Example 68, 4-(5-methyl-2-phenyl-4-oxazolylmethoxy) acetophenone was obtained by reaction of 4-chloromethyl-5-methyl-2-phenyloxazole with p-hydroxyacetophenone. Recryatallization of ethyl acetate-hexane gave colorless crystals.
Melting point: 126-127°C.

Reference Example 88

In substantially the same manner as in Reference Example 1, methyl (E)-3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-butenoate was obtained by reaction of 4-(5-methyl-2-phenyl-4-oxazolylmethoxy) acetophenone with trimethyl phophonoacetate.
Recryatallization of ethyl acetate-ether gave colorless crystals.
Melting point: 125-126°C.

Reference Example 89

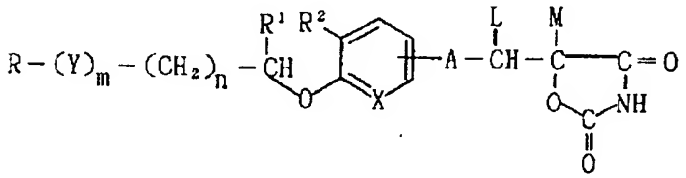
In substantially the same manner as in Reference Example 7, methyl (E)-3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-buten-1-ol was obtained by reduction of methyl (E)-3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-butenoate with diisobutylaluminum hydride. Recryatallization of ethyl acetate-ether gave colorless crystals.
Melting point: 126-127°C.

Reference Example 90

In substantially the same manner as in Reference Example 14, methyl (E)-3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-buten-1-al was obtained by oxidation of (E)-3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-buten-1-ol with manganese dioxide. Recryatallization of ethyl acetate-ether gave colorless crystals.
Melting point: 94-95°C.

Claims

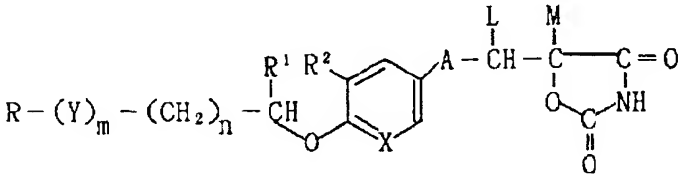
1. 2,4-Oxazolidinedione compounds of the formula (I):



(I)

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH) or -NR^3- (wherein R^3 is an alkyl group, which may itself be substituted); m is O or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each independently hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M are each hydrogen, or L and M combine with each other to form a bond; and
pharmaceutically acceptable salts thereof.

2. 2,4-Oxazolidinedione compounds of the formula (I-A1):



(I-A1)

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH) or -NR^3- (wherein R^3 is an alkyl group, which may itself be substituted); m is O or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each independently hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M are each hydrogen, or L and M combine with each other to form a bond; and
pharmaceutically acceptable salts thereof.

3. A compound as claimed in Claim 2, wherein n is 0 or 1; R is an hydrocarbon group or an heterocyclic group, each of which may independently be substituted; A is a saturated bivalent straight or branched chain hydrocarbon residue having 1 to 4 carbon atoms; L and M are each hydrogen; R^1 and R^2 are each hydrogen, or R^1 and R^2 combine with each other to form a 5-membered heterocyclic group containing nitrogen.

4. A compound as claimed in Claim 3, wherein A is-CH_2CH_2-.

5. A compound as claimed in Claim 3, wherein R is an heterocyclic group, which may be substituted.

6. A compound as claimed in Claim 3, wherein R is an oxazolyl group, which may be substituted.

7. A compound as claimed in Claim 3, wherein R is an oxazolyl group, which may be substituted by phenyl, naphthyl, furyl, thienyl or (C_1-C_3)alkyl.

8. A compound as claimed in Claim 2, wherein Y is -CO-; n is 0; A is a saturated bivalent straight chain hydrocarbon residue having 1 to 4 carbon atoms; and L and M are each hydrogen.

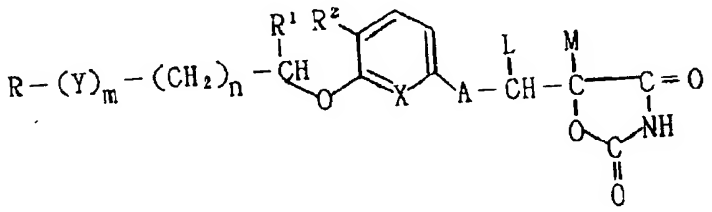
9. A compound as claimed in Claim 8, wherein R^1 and R^2 are each hydrogen.

10. A compound as claimed in Claim 8, wherein A is $-CH_2-$ or $-CH_2CH_2-$.

11. A compound as claimed in Claim 8, wherein X is CH.

12. A compound as claimed in Claim 8, wherein X is nitrogen.

13. 2,4-Oxazolidinedione compounds of the formula (I-A2):



(I-A2)

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH) or $-NR^3-$ (wherein R^3 is an alkyl group, which may itself be substituted); m is O or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M are each hydrogen, or L and M combine with each other to form a bond; and

pharmaceutically acceptable salts thereof.

14. A compound as claimed in Claim 1, wherein the compound is 5-[3-[4-[2-(5-methyl-2-naphthyl-4-oxazolyl)ethoxy]phenyl]propyl]2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

15. A compound as claimed in Claim 1, wherein the compound is 5-[3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

16. A compound as claimed in Claim 1, wherein the compound is 5-[3-[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]propyl]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

17. A compound as claimed in Claim 1, wherein the compound is 5-[3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)-benzofuran-5-yl]propyl]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

18. A compound as claimed in Claim 1, wherein the compound is 5-[3-[2-(2-naphthylmethyl)benzoxazol-5-yl]propyl]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

19. A compound as claimed in Claim 1, wherein the compound is 5-[3-[4-(5-methyl-4-phenyl-2-thiazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

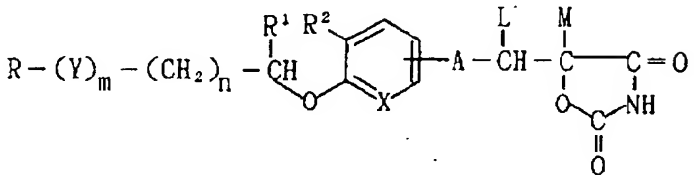
20. A compound as claimed in Claim 1, wherein the compound is 5-[5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]pentyl]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

21. A compound as claimed in Claim 1, wherein the compound is 5-[4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl) ethoxy]phenyl]butylidene]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

22. A compound as claimed in Claim 1, wherein the compound is 5-[3-[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propyl]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

23. A compound as claimed in Claim 1, wherein the compound is 5-[3-[4-[2-(N-methyl-N-(2-pyridyl)amino]ethoxy]phenyl]propyl]-2,4-oxazolidinedione, or a pharmaceutically acceptable salt thereof.

24. A medical composition comprising, as an effective component, a 2,4-oxazolidinedione derivative represented by the general formula (I):

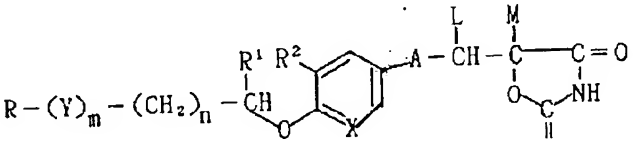


(I),

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH)- or -NR^3- (wherein R^3 is an alkyl group which may itself be substituted); m is 0 or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M are each hydrogen, or L and M combine with each other to form a bond; or

a pharmaceutically acceptable salt thereof.

25. A medical composition comprising, as an effective component, a 2,4-oxazolidinedione derivative represented by the general formula (I-A1):



(I-A1),

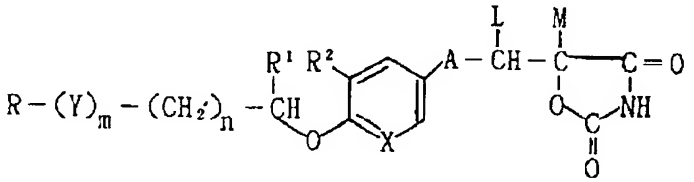
wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH)- or -NR^3- (wherein R^3 is an alkyl group, which may itself be substituted); m is 0 or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M are each hydrogen, or L and M combine with each other to form a bond; or

a pharmaceutically acceptable salts thereof.

26. A medical composition as claimed in Claim 25, which is a therapeutic agent for diabetes.

27. A medical composition as claimed in Claim 25, which is a therapeutic agent for hyperlipemia.

28. The use of a 2,4-oxazolidinedione compound of the formula (A-1):



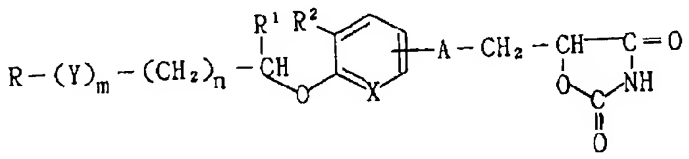
(A-1),

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH)- or -NR^3- (wherein R^3 is an alkyl group which may itself be substituted); m is 0 or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen; L and M are each hydrogen, or L and M combine with each other to form a bond; or

a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for the treatment of a mammal suffering from diabetes or hyperlipidemia.

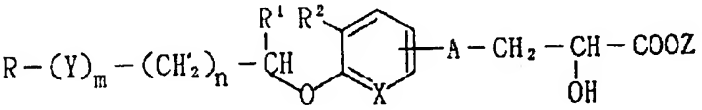
29. A method of producing a 2,4-oxazolidinedione derivative represented by the general formula (I):



(I),

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH) or -NR^3- (wherein R^3 is an alkyl group, which may itself be substituted); m is O or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each independently hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen;

which method comprises reacting a compound represented by the general formula (III):



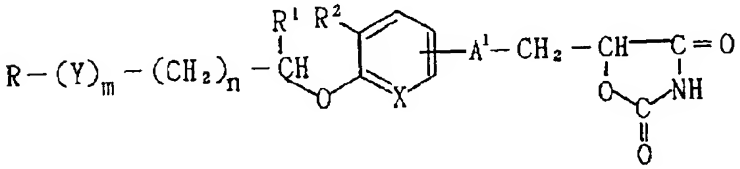
(III),

wherein Z is hydrogen, a lower (C_1-C_4) alkyl group or an aralkyl group, and the other symbols have the meanings defined above,

with an alkali metal cyanate,

followed by allowing the resulting reaction product to be in an acidic condition.

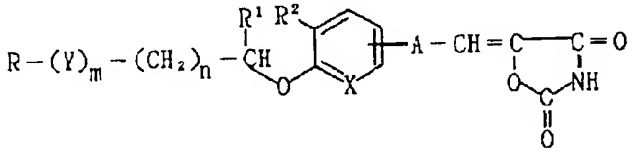
30. A method of producing a 2,4-oxazolidinedione derivative represented by the general formula (I-B2a):



(I-B2a),

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH) or -NR^3- (wherein R^3 is an alkyl group, which may itself be substituted); m is 0 or 1; n is 0, 1 or 2; X is CH or N; A1 is a saturated bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each independently hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen;

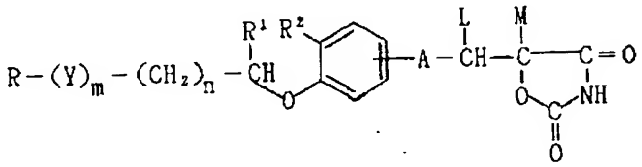
which method comprises reducing a compound represented by the general formula (I-B1):



(I-B1),

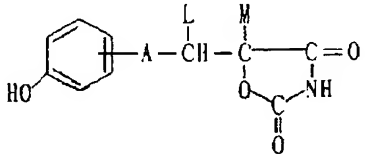
wherein A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms, and the other symbols have the meanings given above.

31. A method of producing a 2,4-oxazolidinedione derivative represented by the general formula:



wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; m is O or 1; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; L and M are each hydrogen, or L and M combine with each other to form a bond,

which method comprises reacting a compound represented by the general formula (V):



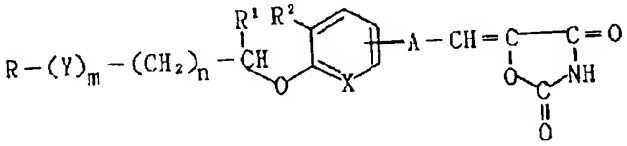
(V),

wherein each symbol has the meaning given above, with a compound represented by the general formula (VI):

$$R\text{-}(CO)_m\text{-}CH_2Q \qquad (VI),$$

wherein Q is a leaving group, and the other symbols have the meanings given above.

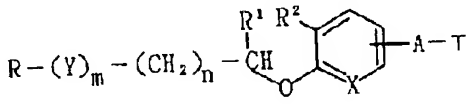
32. A method of producing a 2,4-oxazolidinedione derivative represented by the general formula (I):



(I)

wherein R is an hydrocarbon residue or an heterocyclic group, each of which may independently be substituted; Y is -CO-, -CH(OH) or -NR^3- (wherein R^3 is an alkyl group, which may be substituted): m is O or 1; n is 0, 1 or 2; X is CH or N; A is a bivalent straight or branched chain hydrocarbon residue having 1 to 7 carbon atoms; R^1 and R^2 are each independently hydrogen or an alkyl group, or R^1 and R^2 combine with each other to form a 5- to 6-membered heterocyclic group, optionally containing nitrogen;

which method comprises reacting with 2,4-oxazolidinedione a compound represented by the general formula:



wherein T is a formyl residue or -CH_2-$CH(B)_2$ (wherein B is a lower (C_1-C_4) alkoxy, lower (C_1-C_4) alkylthio or lower (C_1-C_4) acyloxy, or two B's combine together to form an ethylenedioxy, trimethylenedioxy or dithiotrimethylene ring), and the other symbols have the meanings given above.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 1341

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
D,Y	WO-A-92 02520 (BEECHAM) 20 February 1992 * claims 1,16 *	1-28	C07D413/12 A61K31/42 C07D417/12 A61K31/425 A61K31/44 C07D413/14 //(C07D413/12, 263:00,263:00)
Y	EP-A-0 428 312 (PFIZER INC.) 22 May 1991 * claims 1,9 *	1-28	
Y	US-A-5 037 842 (GOLDSTEIN) 6 August 1991 * claims 1,8,9 *	1-28	
A	WO-A-92 18501 (UPJOHN COMPANY) 29 October 1992 * claim 1 *	1-28	
A	EP-A-0 441 605 (SANKYO COMPANY LIMITED) 14 August 1991 * claims 1,26 *	1-28	
A	JP-A-4 225 978 (SANKYO COMPANY LIMITED) 14 August 1992 Also see equivalent WPI abstract.	1-28	
A,P	JP-A-5 202 042 (SANKYO COMPANY LIMITED) 10 August 1993 Also see equivalent WPI abstract	1-28	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)
C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	3 May 1994	Gettins, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)